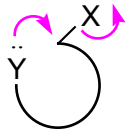
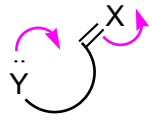
1 Cyclization methods

In a cyclization process the the ring is made by the formation of one new bond in an intramolecular reaction; for example, by nucleophilic attack on an electrophilic atom. The various possible ways of doing this are illustrated.

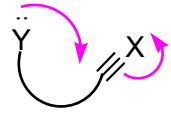
Nomenclature of ring closure



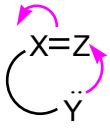
exo-tet



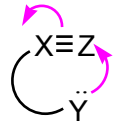
exo-trig



exo-dig



endo-trig

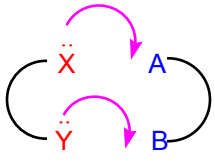


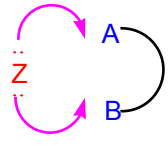
endo-dig

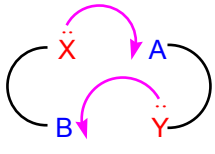
Some of these processes are more likely than others for steric reasons. For example, five membered rings are not often formed by endo-trig cyclization but 5-endo-dig reactions are more common.

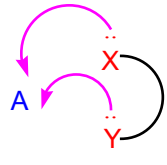
Of course, practical ring syntheses rarely involve the formation of a ring from just a single precursor molecule. In most syntheses the precursor is assembled in situ from two or more "building blocks".

Examples of two component cyclisation reactions



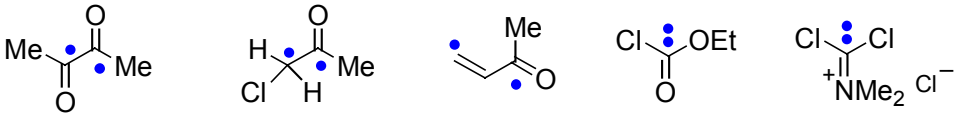




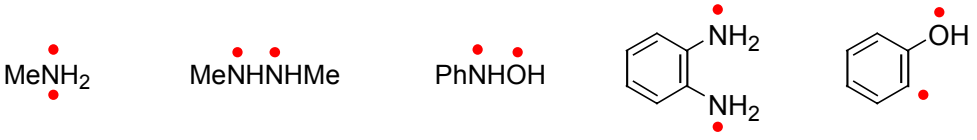


Typical "building blocks" for cyclization reactions

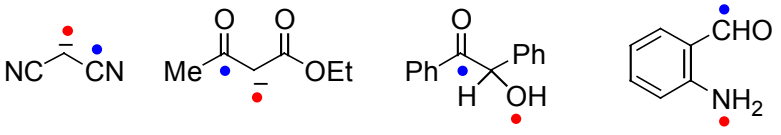
bis-electrophiles



bis-nucleophiles

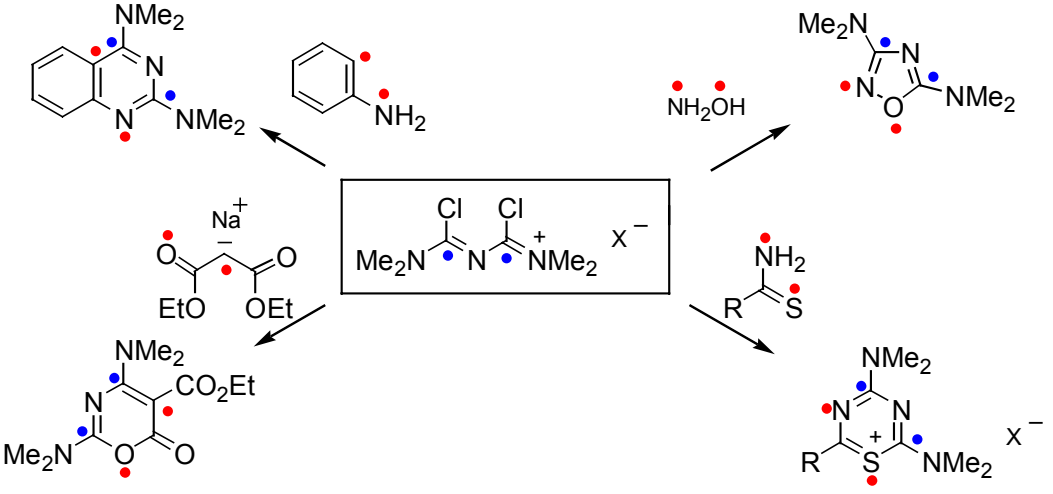


"nucleophile + electrophile" combinations



There is a vast range of simple building blocks, of which only a few are illustrated. Carbonyl groups are the most common electrophilic components, and carbanions, nitrogen, oxygen and sulfur functions the most common nucleophilic components.

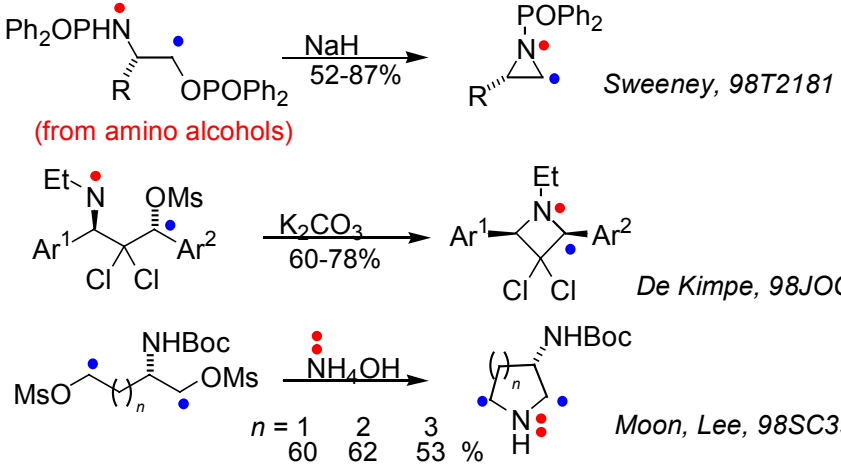
Here is just one example of how a building block (a bis-electrophile) can act as a source of several different heterocycles.



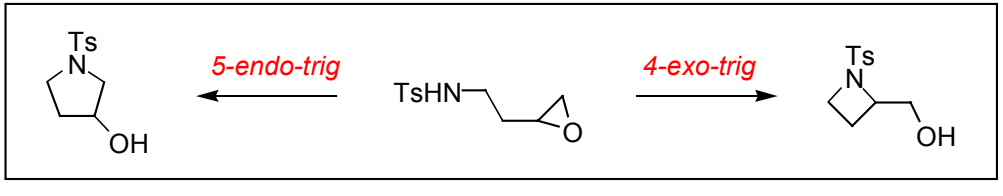
Review: Liebscher, 88S655

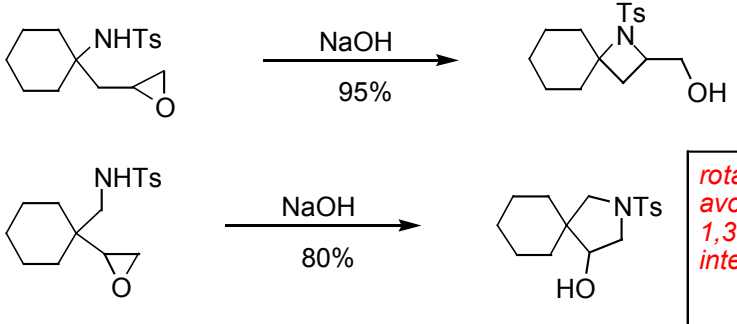
Saturated heterocycles by intramolecular S_N2 reaction

Easy: 3, 4, 6 membered rings
More difficult: 4 membered rings (need buttressing groups);
7 membered and larger rings



When alternative modes of cyclization are possible steric effects determine the structure of the product:

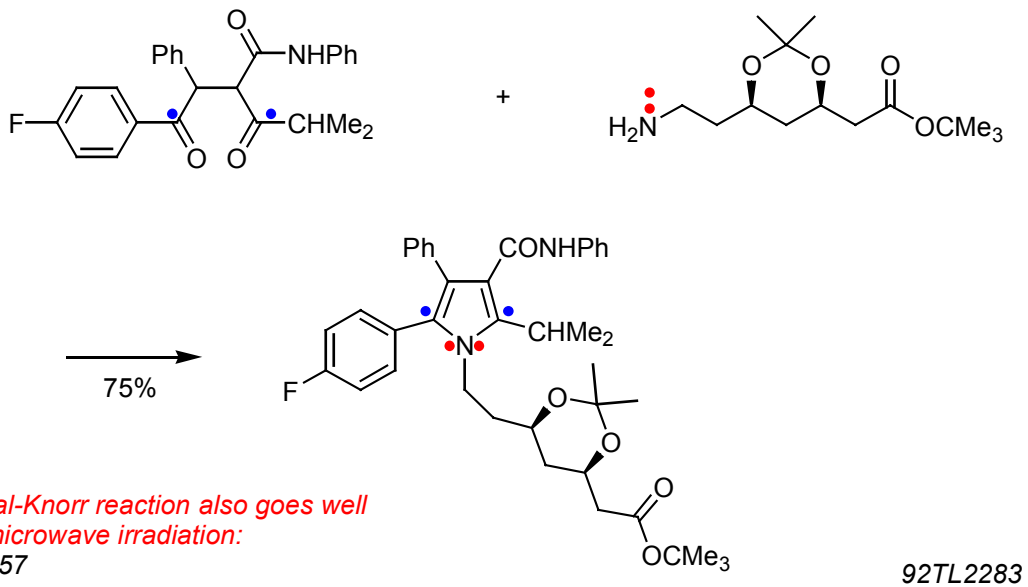




93TL2315

Carbonyl components as electrophiles: examples of pyrrole synthesis with amines as the nucleophiles

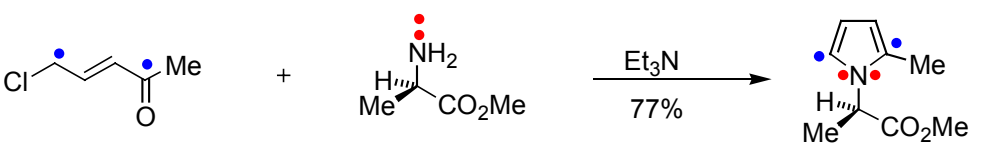
The Paal–Knorr synthesis is the reaction of 1,4-dicarbonyl compounds with amines. It is a very tolerant method, as shown by this example of the synthesis of a sterically crowded pyrrole.



The Paal-Knorr reaction also goes well under microwave irradiation:
99TL3957

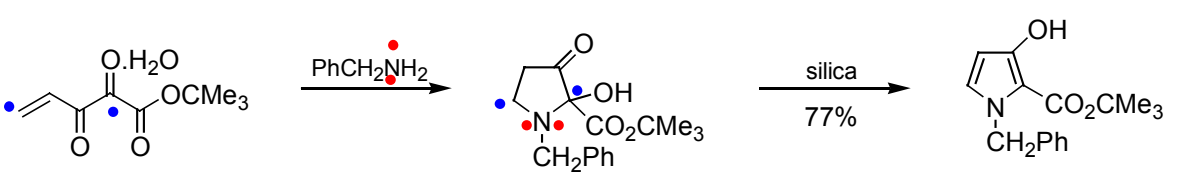
92TL2283

γ-Chloroenones react with esters of α-amino acids to give chiral pyrroles.



97T(AS)753

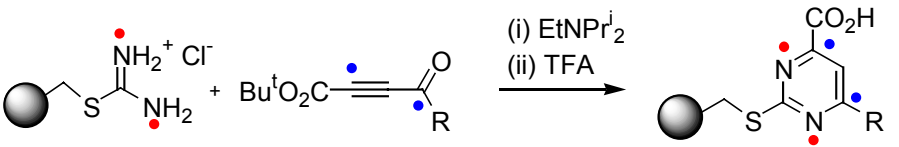
Vicinal tricarbonyl compounds are excellent reagents for the synthesis of pyrrolidinones and hydroxypyrroles.



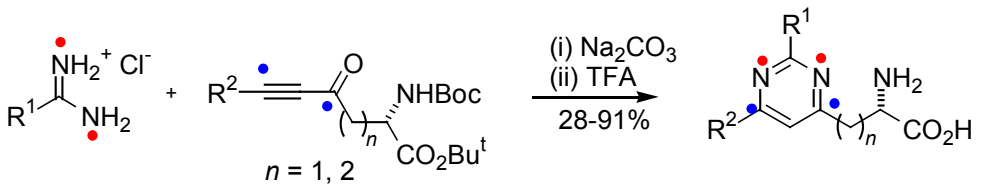
89JA371

Other ring systems can be created by the addition of a variety of bis(nucleophiles) to enones and ynones; an example is shown.

A recent pyrimidine synthesis based on a bis(electrophile) plus bis(nucleophile) combination

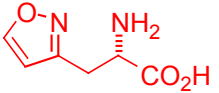


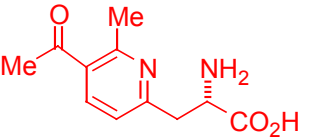
Obrecht et al., 97HCA65



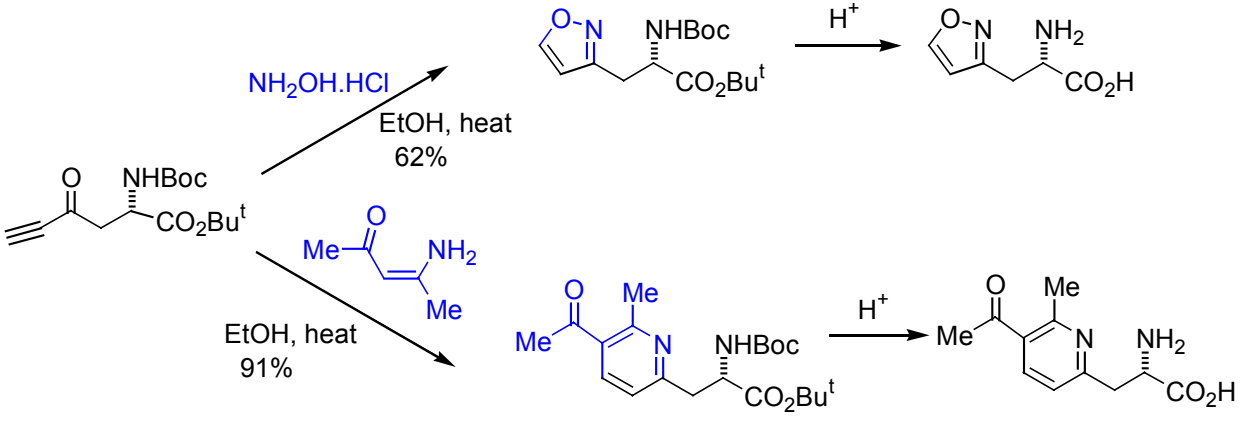
Adlington, Baldwin et al., 97CC1757, 99JCS(P1)855

Problem: **Use the above methodology to devise routes to the following heterocyclic amino acids:**





Answer:

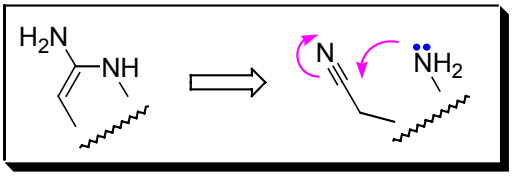


Adlington, Baldwin et al., 00JCS(P1)303

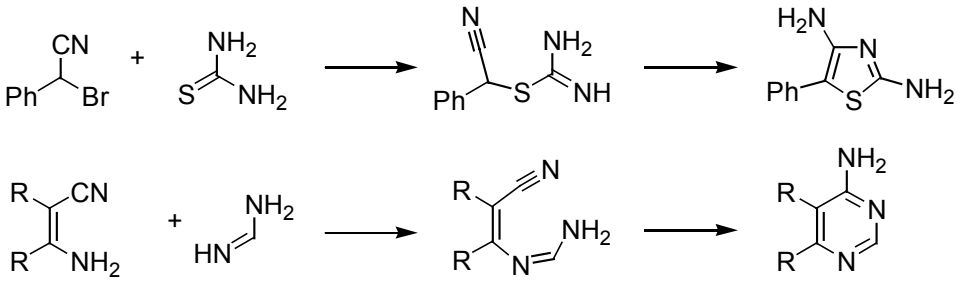
Cyclization on to cyano groups and arynes

Attack on cyano groups, especially by nitrogen nucleophiles, is a common method for the formation of C-amino substituted nitrogen heterocycles.

Cyclization on to cyano groups

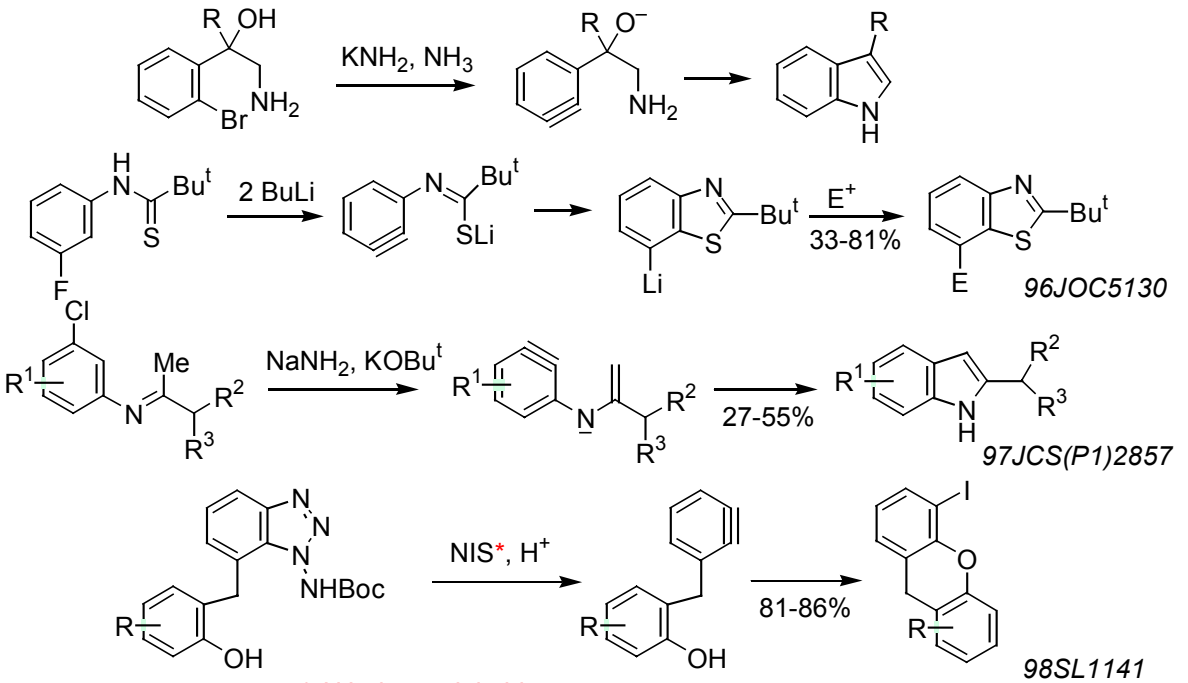


e.g.



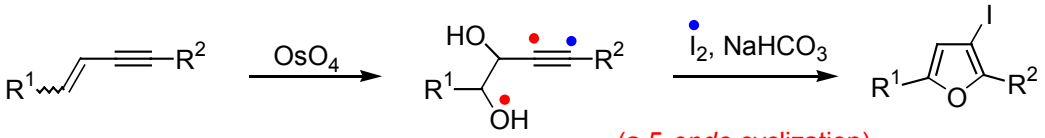
Cyclization on to arynes is useful for making some benzo fused heterocycles.

Cyclization by addition to aryne intermediates



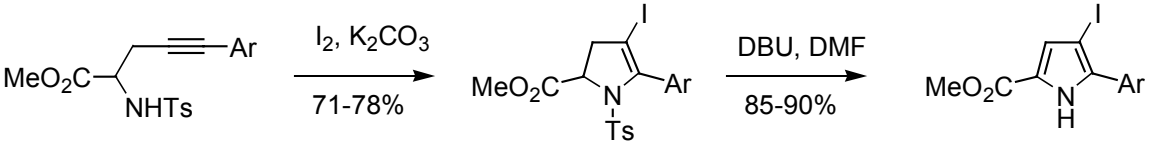
In the last example, note that the aryne cyclization is accompanied by electrophilic iodination. This "iodocyclization" can also be used to generate other heterocycles. Iodine is a useful substituent because it can be replaced by other groups, using palladium coupling or radical methods (for an example see 99SL1432).

Iodocyclization routes to furans and pyrroles

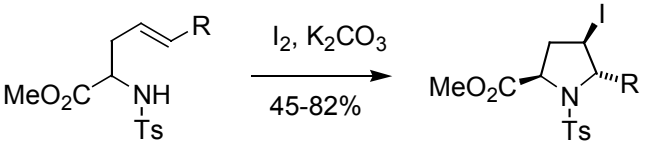


(a 5-*endo* cyclization)

Bew, Knight, 96CC1007



Knight et al., 98CC2207

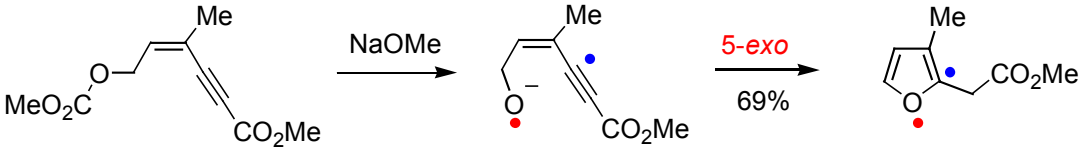


(Note the relative stereochemistry at C-2 and C-5 which results from kinetically controlled addition; it is reversed under acid conditions)

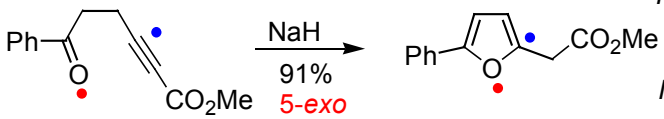
Knight et al., 98SL731

Simple cyclizations on to triple bonds are also useful:

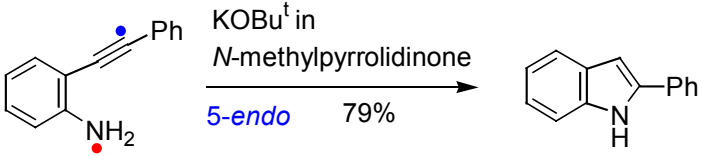
Some cyclizations on to triple bonds



Marshall, DuBay, 93JOC3602
Related: 94JOC6110; 95JOC5966

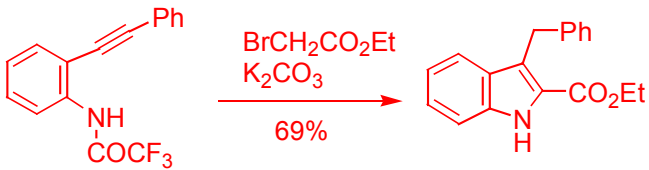


Nicola et al., 00EJO527

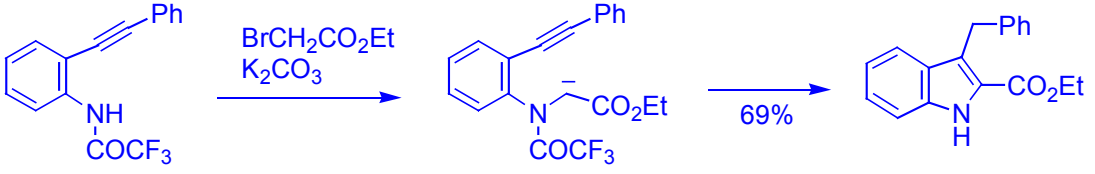


Rodriguez et al., 00AG(E)2488

***Problem:* Suggest a mechanism for the following:**

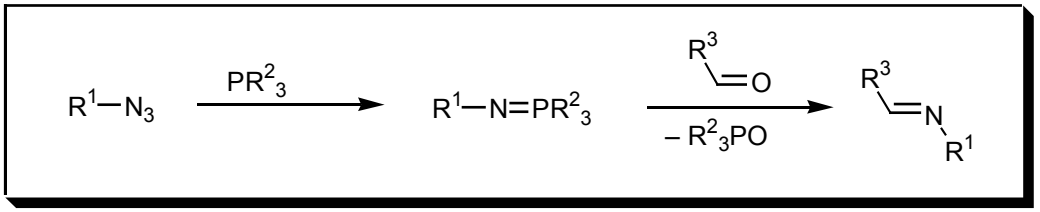


Answer: **This is an *N*-alkylation followed by a 5-*exo*-*dig* cyclization. The $COCF_3$ group is lost by hydrolysis.**

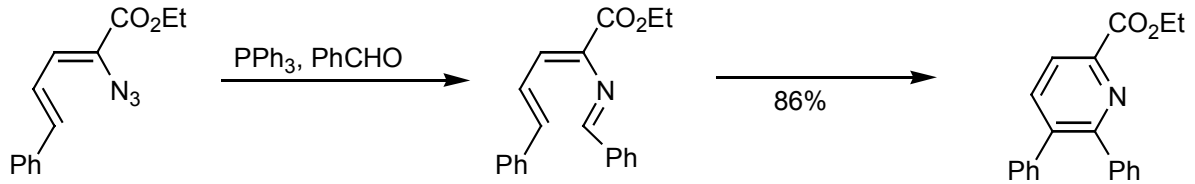


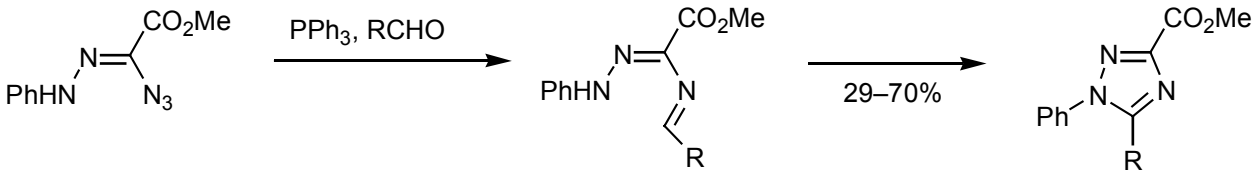
Arcadi et al., 00SL647

The aza Wittig reaction

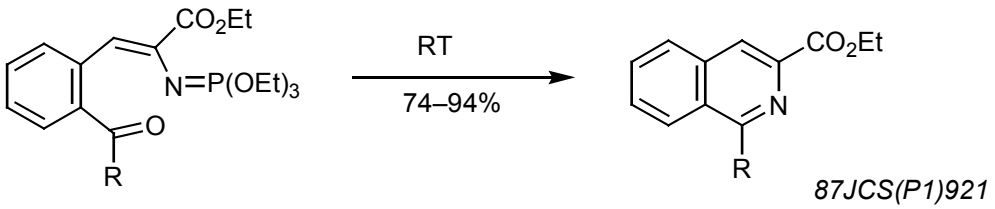


Reviews: 94S1197, 95AHC(64)159

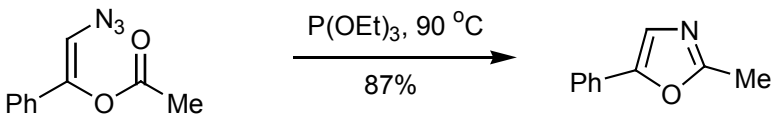




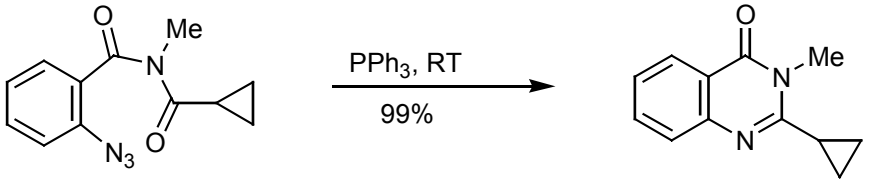
The intramolecular aza Wittig reaction



87JCS(P1)921



89JOC431

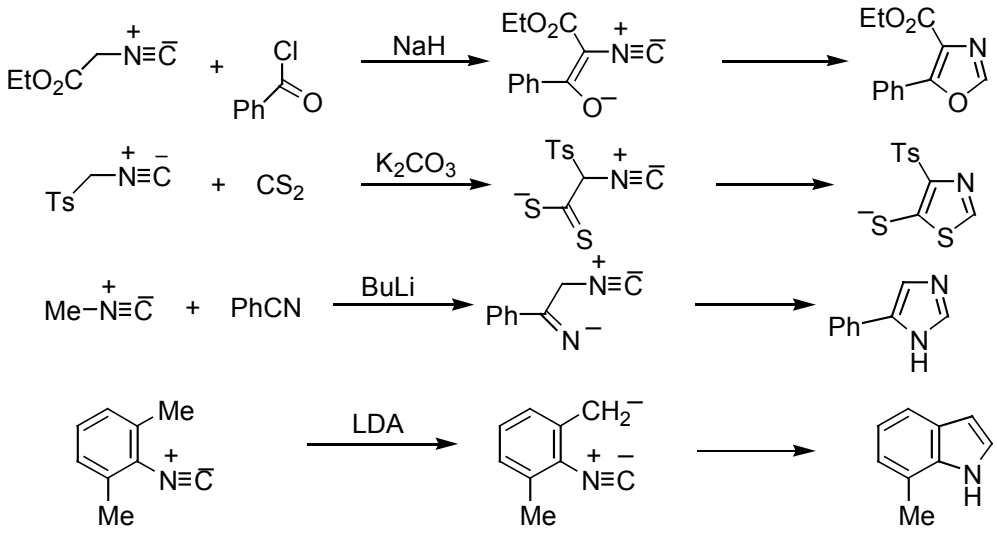


89TL3313

Reviews: 94S1197, 95AHC(64)159

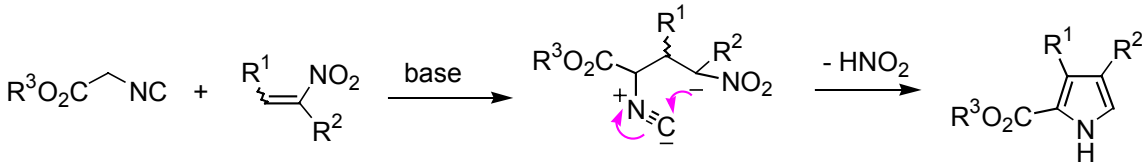
Cyclizations on to isocyanides

Isocyanides are very useful building blocks for 5-membered heterocycles. The substitution patterns of the products (no substituent at C-2 but substituents at other positions) are difficult to achieve by other methods. They can be represented as 5-endo-dig cyclizations.



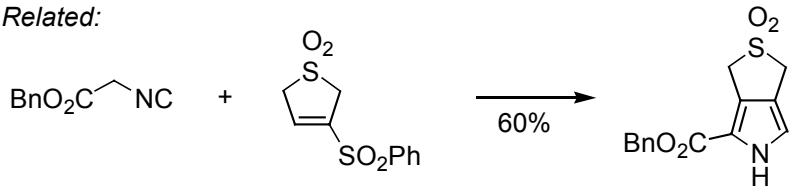
Review: Maraccini, Torroba,93OPP(25)141

The Barton-Zard pyrrole synthesis and related methods

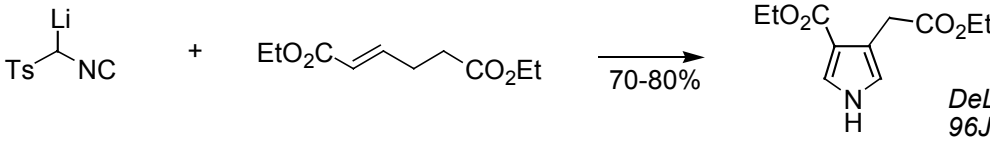


Review: Maraccini, Torroba,93OPP(25)141
Recent examples: Lash et al., 98JOC3998, 8455

Related:

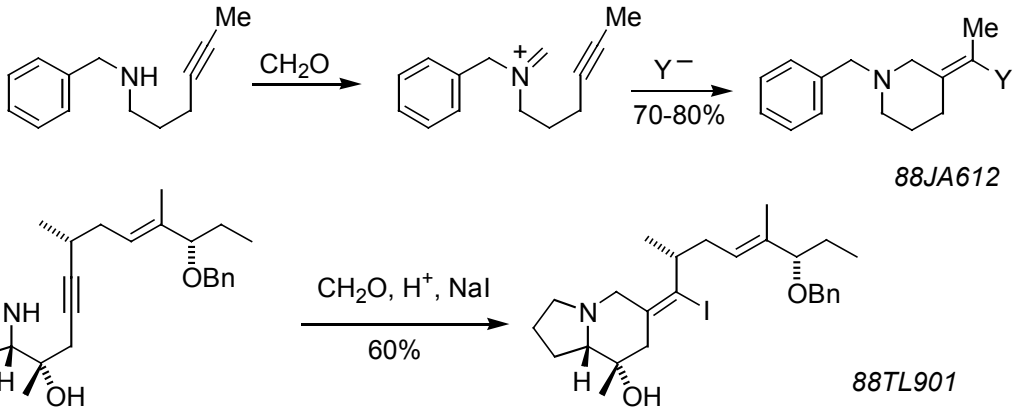


Abel et al., 98HCA1978



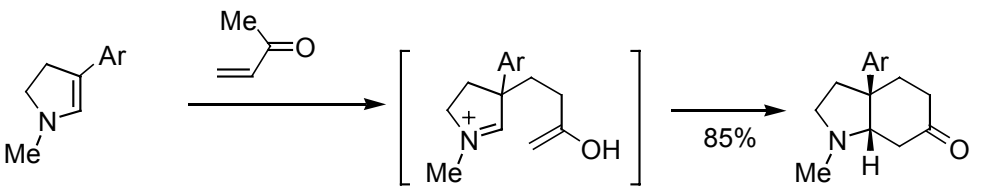
DeLeon, Ganem. 96JOC8730

Iminium ion cyclizations



88JA612

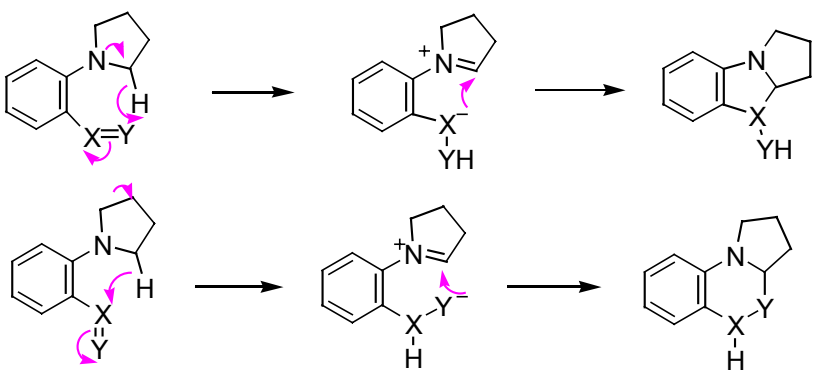
88TL901



77ACR193

Review: Overman, Ricca, 91COS(2)1007

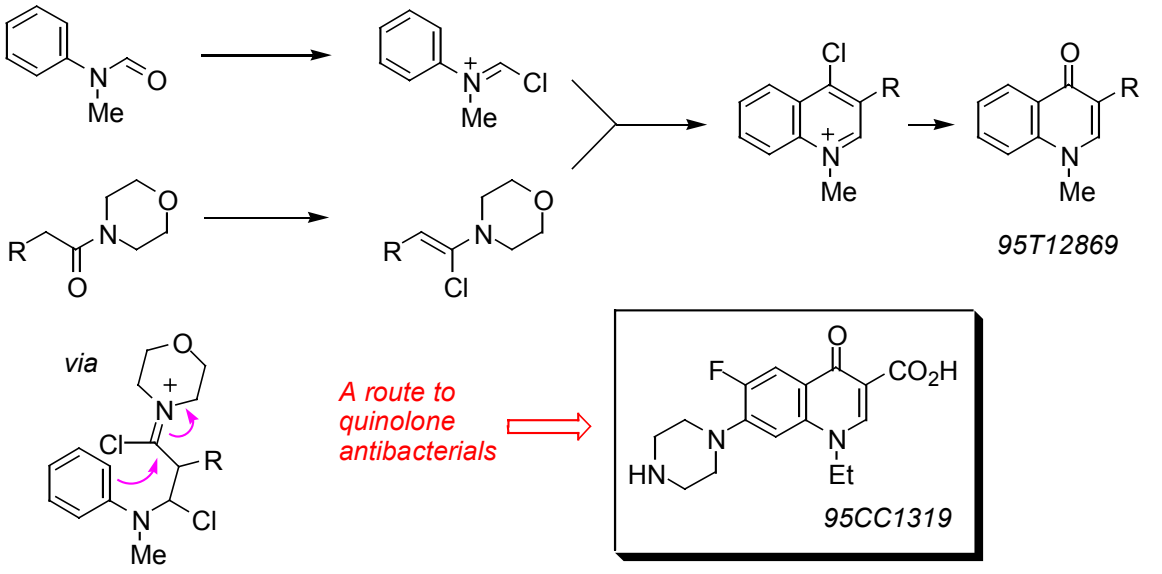
Iminium ion cyclizations: the "*tert*-amino effect"



X=Y = C=C, C=N, C=O, C=S, N=N, N=O, N=S

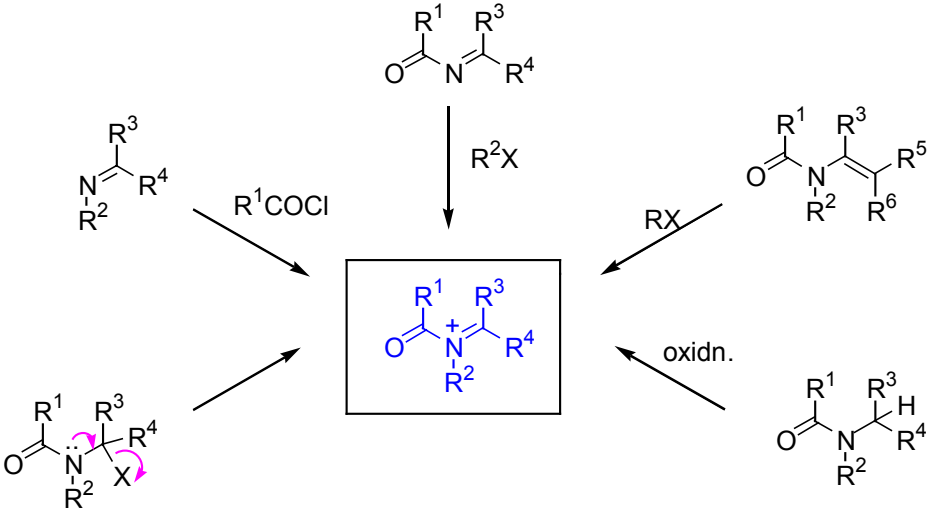
Review and examples: Meth-Cohn, 96AHC(65)1

The "reverse Vilsmeier" route to quinolines and quinolones



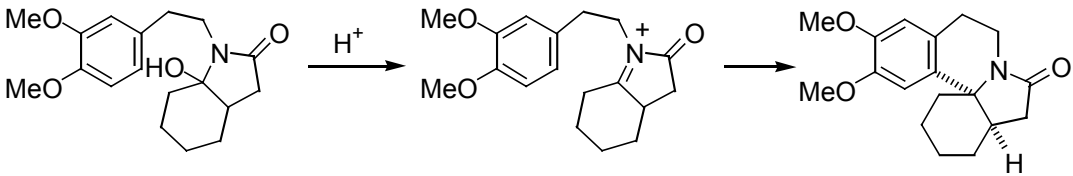
Review: 93H(35)539

Methods of generation of acyliminium ions

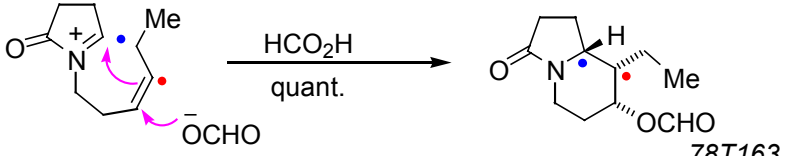


Review: Heimstra,Speckamp,91COS(2)1047

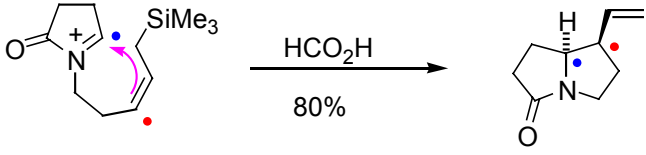
Cyclization of acyliminium ions



59CB(91)1461,1472



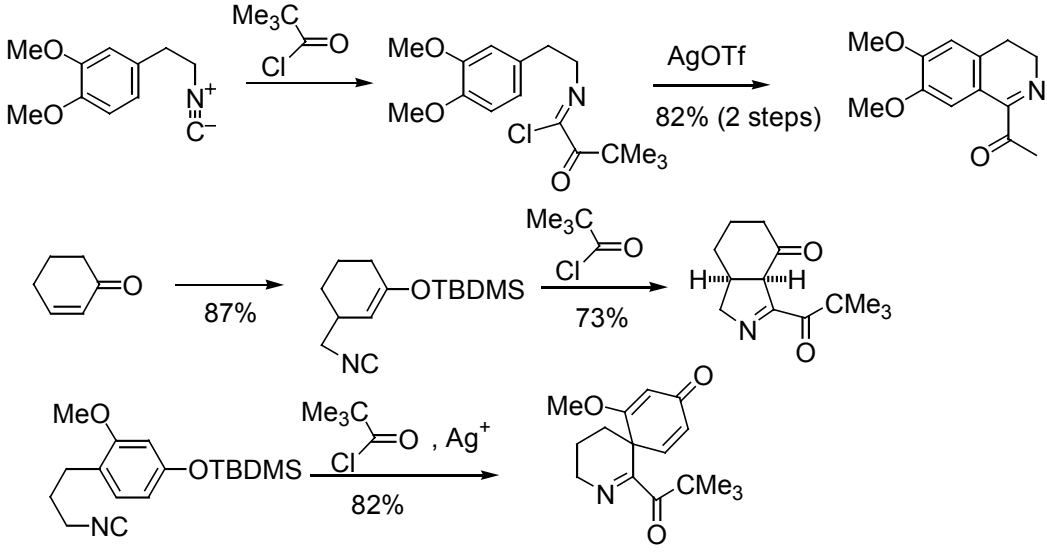
78T163



85JOC4014

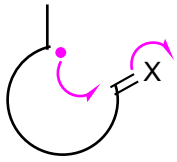
Note the effect of changing Me to $SiMe_3$ in these two reactions; $SiMe_3$ stabilizes a β cation:

Cyclization of *C*-acylnitrilium ions derived from isocyanides



Review: Livinghouse, 99T9947

Radical cyclization: general principles



exo cyclization generally preferred (kinetic control)

5-*exo-trig* cyclizations are the most common

6 membered rings can be formed by *exo* or *endo* cyclization

smaller and larger ring sizes possible if stereochemistry is right and/or if new radical is stabilized

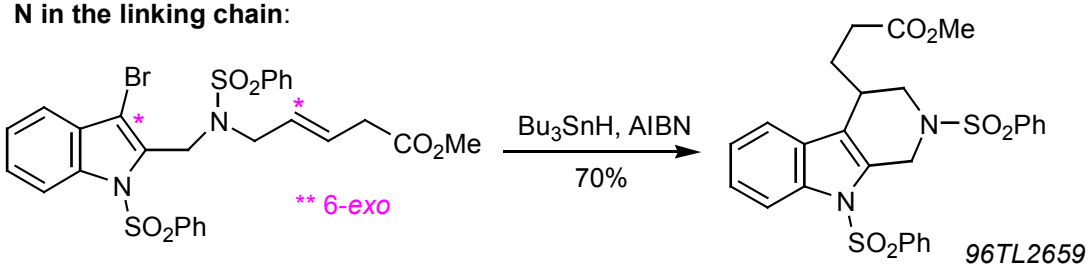
For heterocyclic synthesis the heteroatom can be located:

in the linking chain (most common)
at the radical center (usually nitrogen radical)
at the center being attacked (rare)

For recent examples of heterocyclic synthesis by radical cyclization see Bowman et al., 00JCS(P1)1.

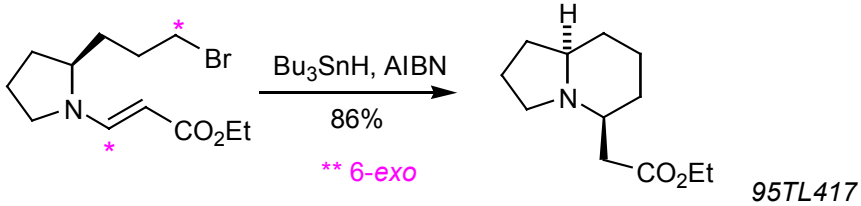
Examples of radical cyclization to give nitrogen heterocycles

N in the linking chain:



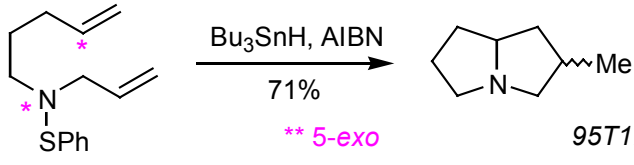
96TL2659

N in the linking chain (bridgehead):



95TL417

N as the radical center:



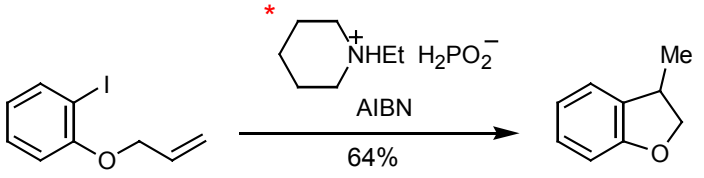
95T1275,1295

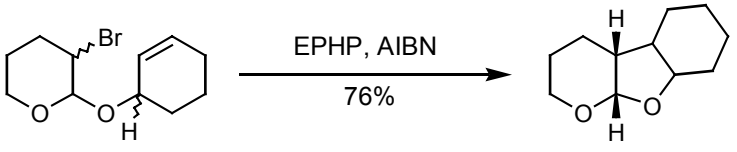
Review:
Fallis and Brinza, 97T17543

Note that all these methods use the same procedure to generate the initial radical: abstraction of a heteroatom by the $Bu_3Sn•$ radical derived from Bu_3SnH. Since tin residues can be difficult to remove from reaction products, and for environmental reasons, alternative methods have been sought.

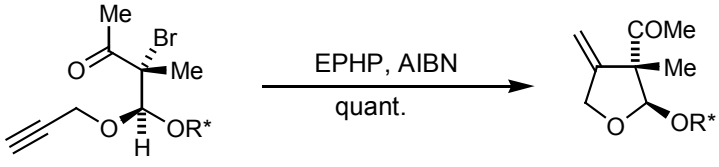
Hypophosphites: Benign alternatives to Bu_3SnH

(* = EPHP)





Murphy, 99TL2415

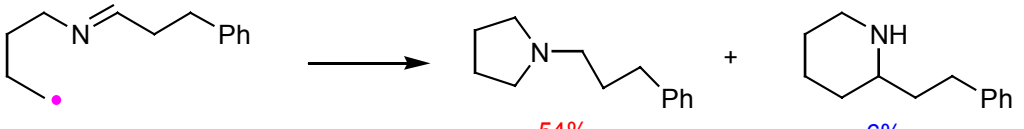


[R* = tetraacetyl-β-D-glucopyranosyl]

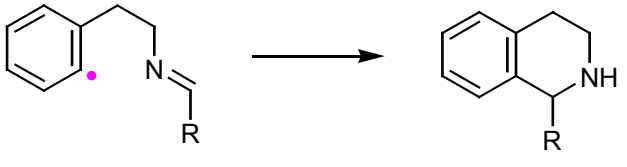
Stoodley, 98CC2691

Cyclization of carbon radicals on to imines

Alkyl radicals: competition between 5-*exo-trig* and 6-*endo-trig*; *e.g.*

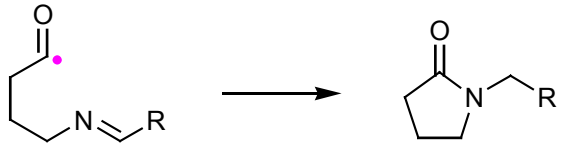


Aryl radicals: strong preference for 6-*endo-trig*



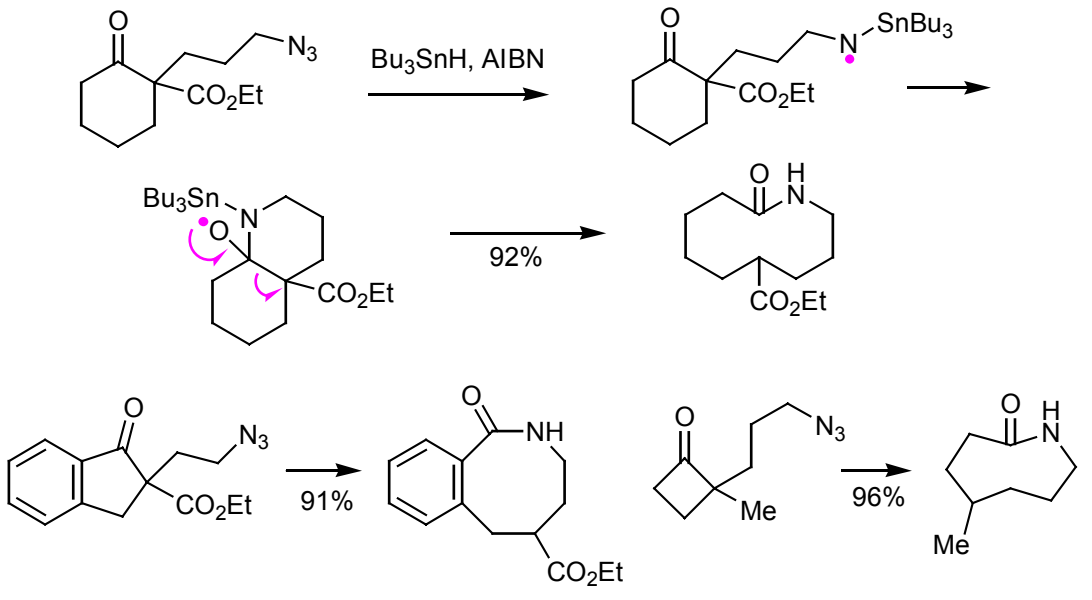
Review: Aldabbagh and Bowman, Contemp. Org. Synth., 1997, 4, 261

Acyl radicals: strong preference for 5-*exo-trig*



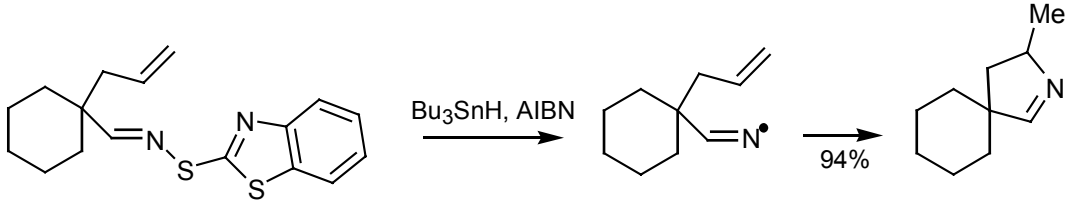
Ryu et al., 98JA5838

Cyclization of nitrogen radicals derived from azides

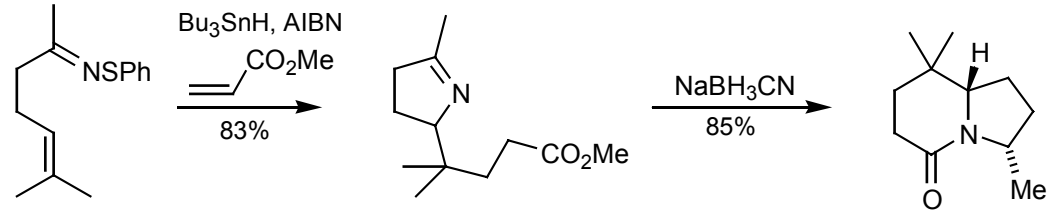


Kim, 93JA3328

Cyclization of iminyl radicals

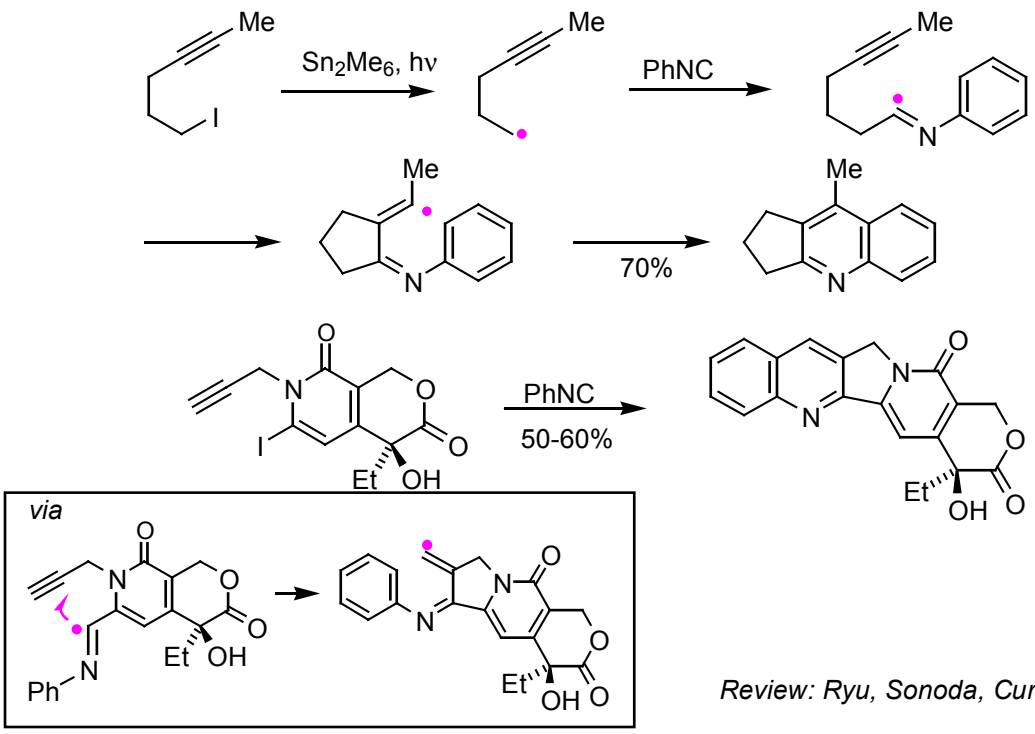


(from the aldehyde and $BthSNH_2$)



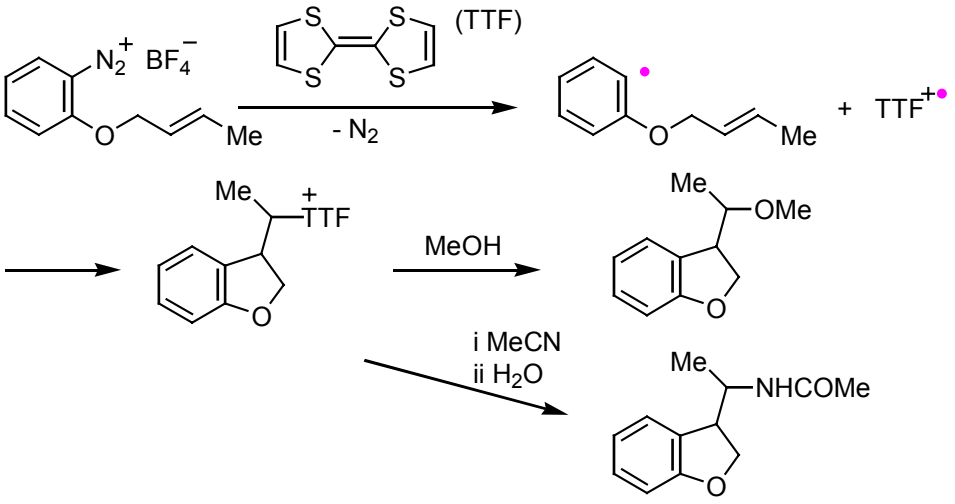
Review: Zard, 96SL1148

Tandem radical cyclization using isocyanides



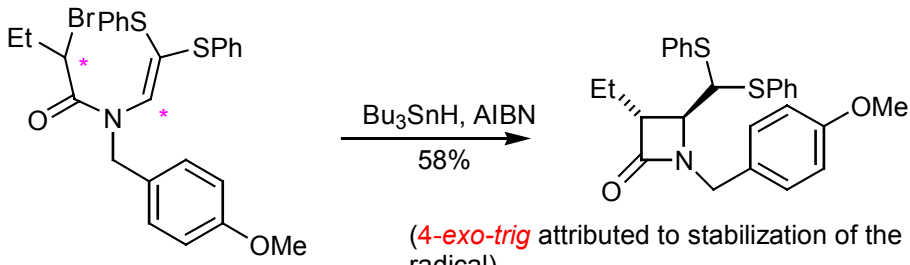
Review: Ryu, Sonoda, Curran 96CRV177

Radical cyclization from diazonium cation electron transfer



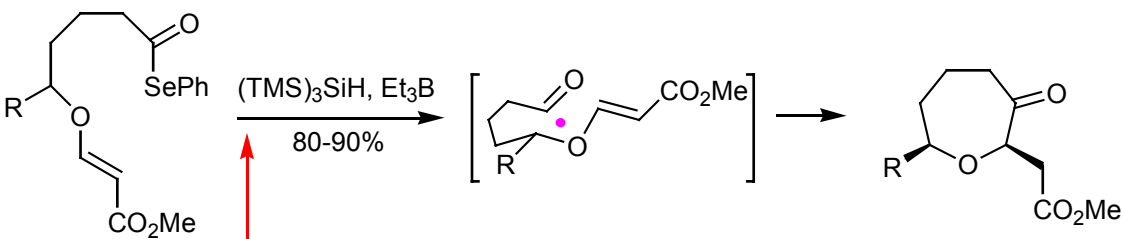
Murphy, 98JCS(P1)2331

Examples of four- and seven-membered ring synthesis by radical cyclization



(4-*exo-trig* attributed to stabilization of the intermediate radical)

Ishibashi et al., 95JOC1276; 96T489

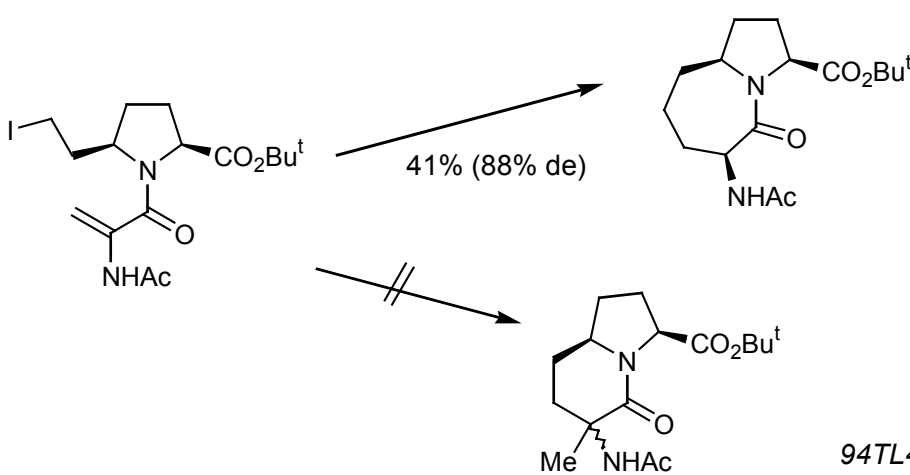


note use of this as an alternative to Bu_3SnH

Evans et al., 96JOC2252, 4880

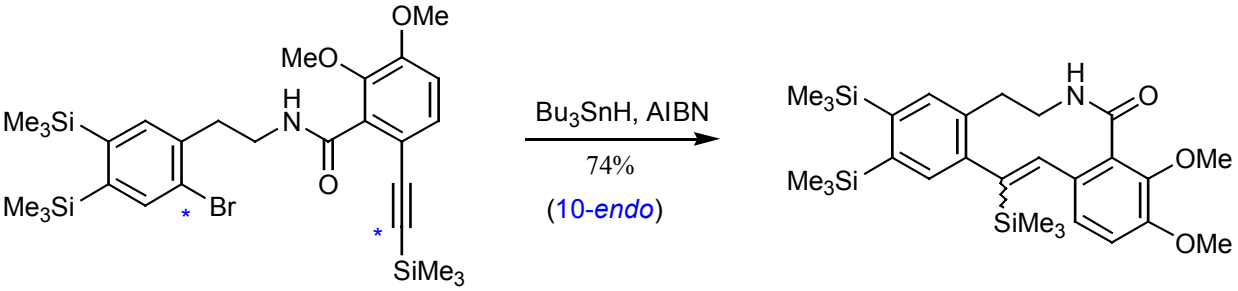
7-*endo* Radical cyclisation preferred over 6-*exo*

"Abnormal" mode because radical is highly stabilized

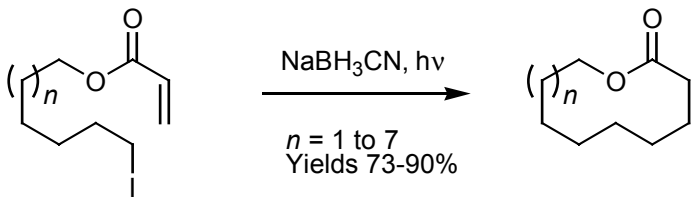


94TL4031

Macrocycles by radical cyclization



96JOC2780

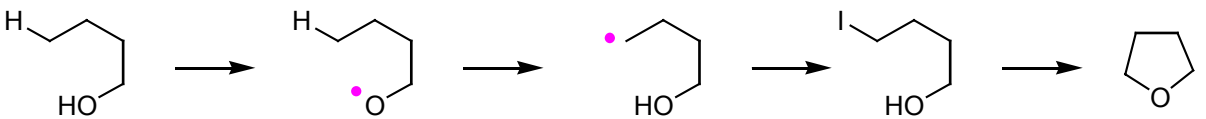


94CL1789

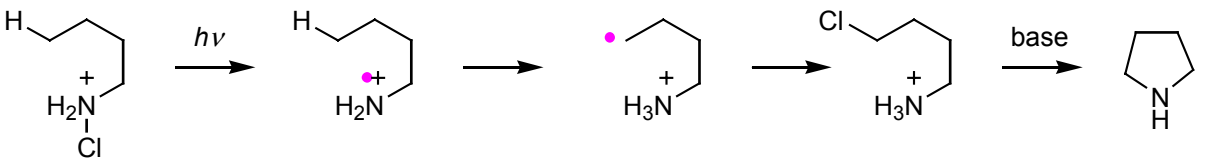
Review: Handa and Pattenden, Contemp. Org. Synth., 1997, 4, 196

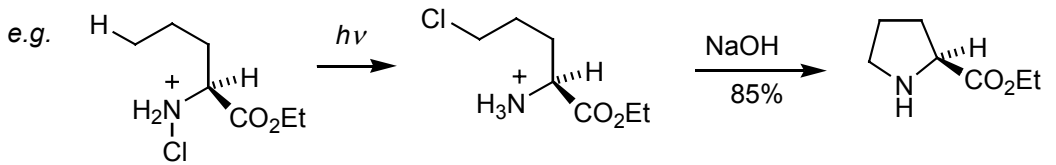
Cyclization following H atom abstraction

1 Tetrahydrofurans from alcohols, iodine and $Pb(OAc)_4$ or $PhI(OAc)_4$/*hν*



2 Pyrrolidines from *N*-chloroamines (Hofmann-Löffler-Freytag reaction)



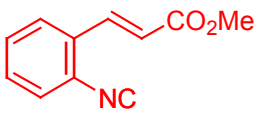


80T2961

Review: Majetich, Wheless, 95T7095

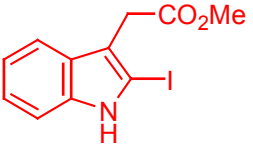
Problems: **Explain the following:**

(a)

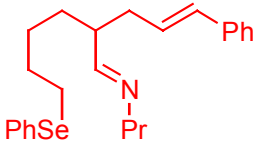


(i) Bu_3SnH/AIBN
(ii) I_2

91%

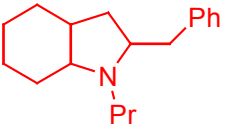


(b)



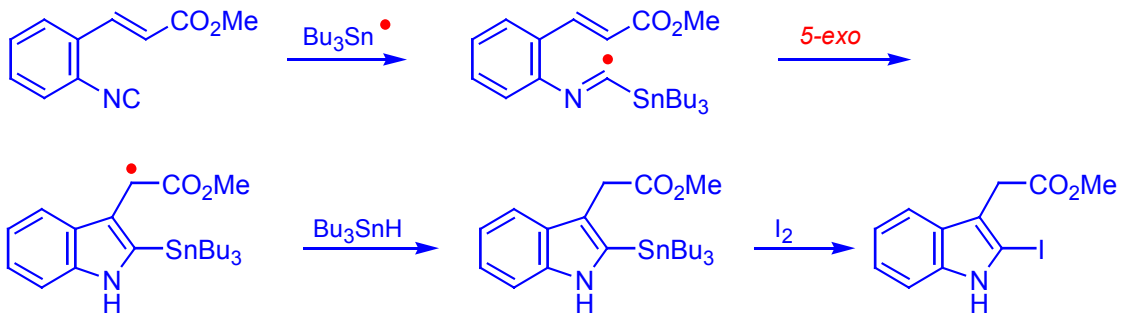
Bu_3SnH/AIBN

57%



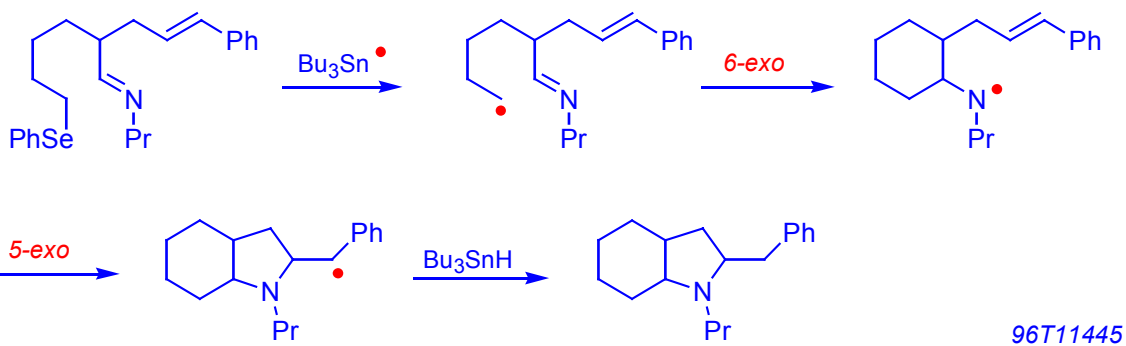
Answers:

(a)



00S429

(b)



96T11445

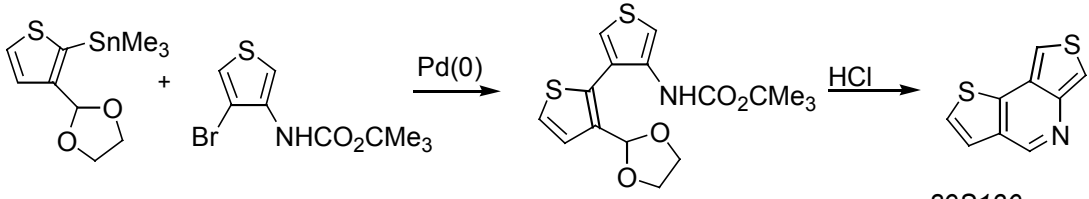
Palladium catalyzed cyclizations

Palladium catalyzed reactions are of rapidly growing importance in heterocyclic chemistry, both for creating ring systems and for substitution reactions. A recently published book provides an overview of the area: "Palladium in Heterocyclic Chermistry" by Jie Jack Li and Gordon W. Gribble, Pergamon, Amsterdam, 2000.

Palladium methodology is widely used to create carbon-carbon bonds between sp^2-sp^2 and sp^2-sp centers. When these reactions are intermolecular they lead to the formation of intermediates that in some cases can then be cyclized by a variety of methods to produce a further ring system. When the reactions are intramolecular (most commonly, intramolecular Heck reactions) a new ring system is produced directly by the palladium catalyzed reaction.

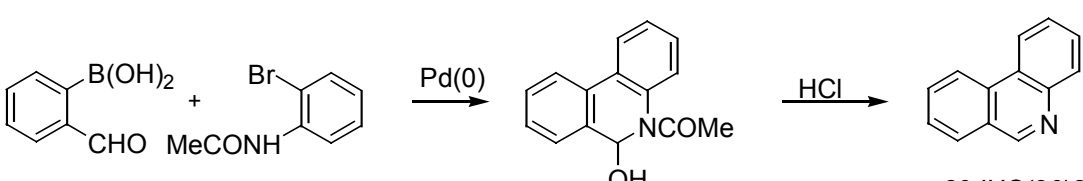
Coupling reactions

Stille coupling followed by cyclization:



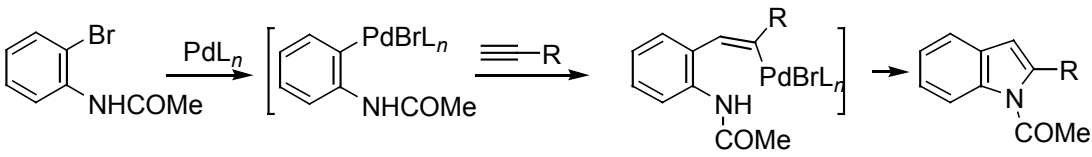
89S130

Suzuki coupling followed by cyclization:

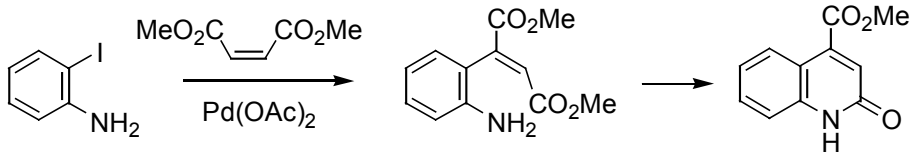


89JHC(26)865

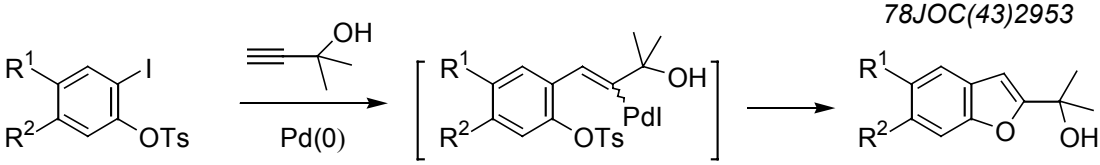
Heck reactions



88H(27)2225; 89JOC(54)5856

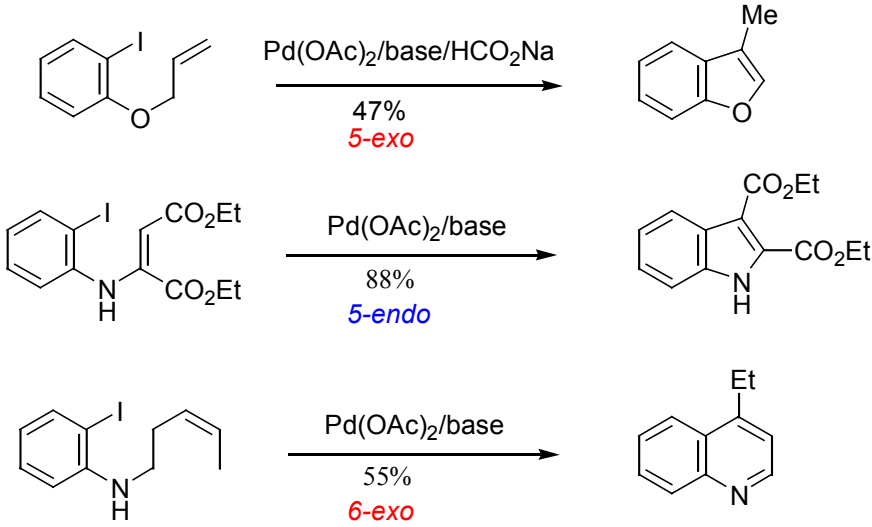


78JOC(43)2953



96H(43)101

Intramolecular Heck reactions

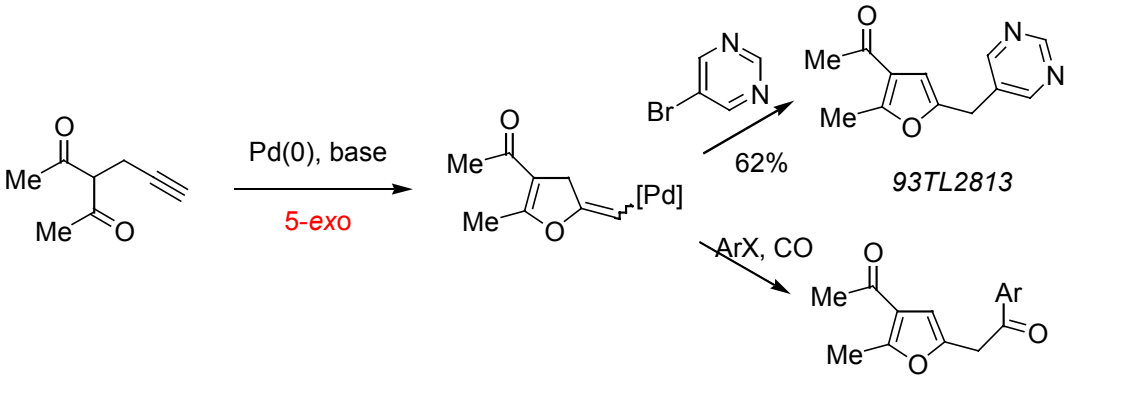


Review: Gibson, Middleton, Contemp. Org. Synth., 1996,3, 447

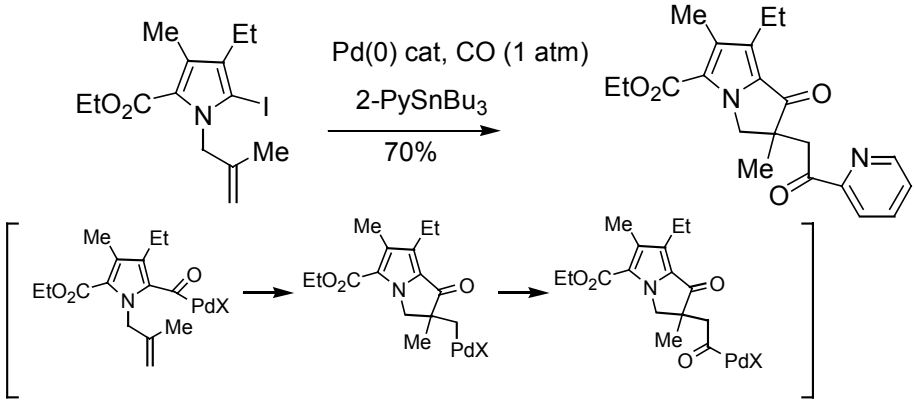
Palladium catalyzed cyclization and functionalization

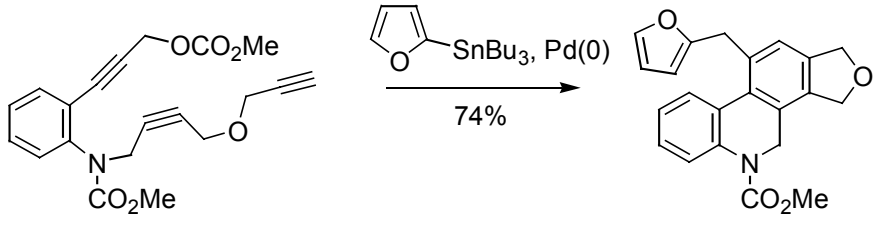
A most useful aspect of palladium catalyzed cyclization is that the organopalladium intermediate produced in the cyclization step can be further substituted. This can lead to functionalization of the heterocycle, to carbonylation followed by further functionalization, or to the formation of one or more new ring systems (cascade reactions).

Cyclization and functionalization



Cascade reactions

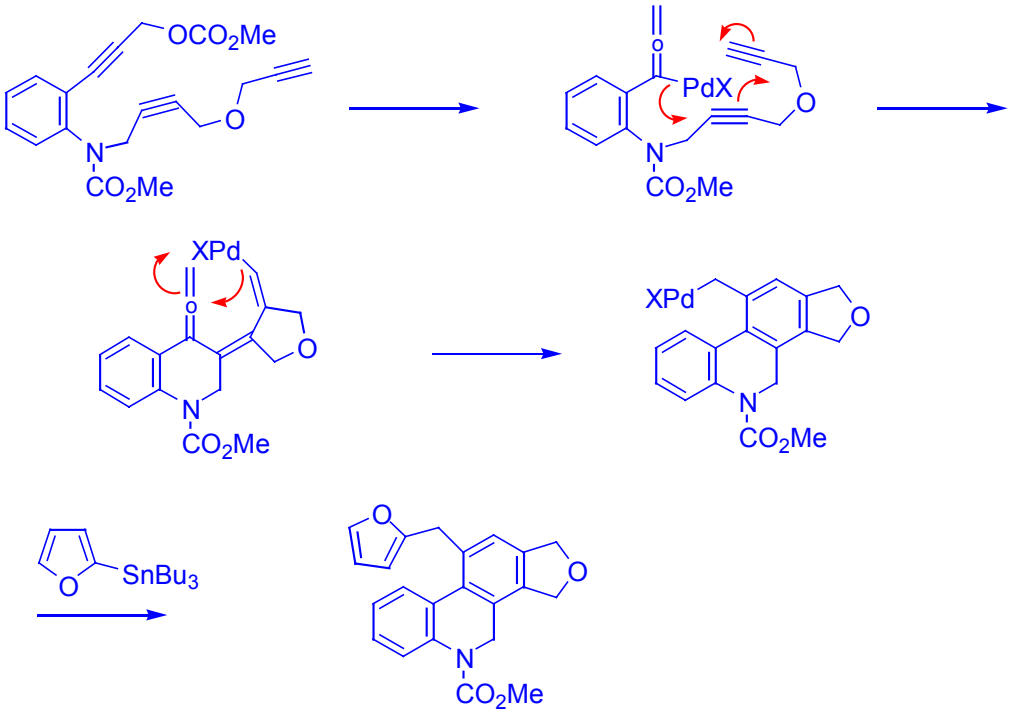




Review: Grigg, Sridharan, 98PAC1047

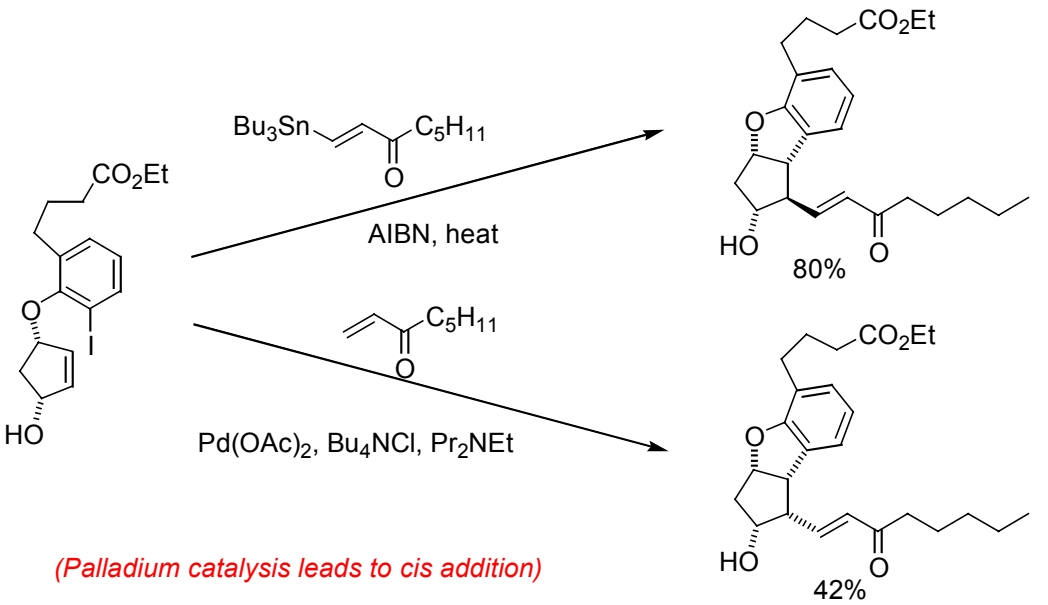
Problem: Write a mechanism for the last reaction.

Suggested answer:



There are some similarities between radical and palladium catalyzed cyclizations. One key difference is the stereochemistry in functionalization reactions, as the following example illustrates.

A comparison of radical and palladium catalyzed cyclization

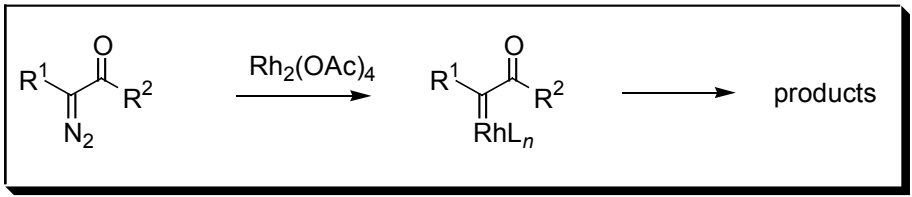


(Palladium catalysis leads to cis addition)

91JOC6253

Rhodium carbenoids from diazocarbonyl compounds

Diazocarbonyl compounds can be decomposed by catalytic amounts of $Rh_2(OAc)_4$ and other rhodium salts.



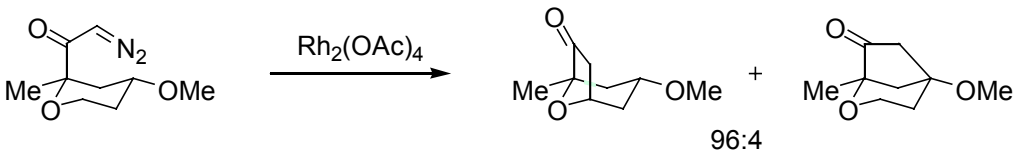
The intermediate rhodium carbenoids produce heterocycles by one of three general processes:

- **Insertion** ***into CH, NH or OH bonds.***
- **Addition** ***to C=C or C=N bonds.***
- **Ylide formation** ***by attack on heteroatoms, often followed by*** **rearrangement**.
  (Substrates are ethers, sulfides, tertiary amines, carbonyl compounds, nitriles, etc.).

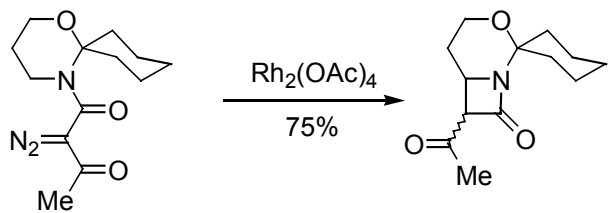
Review: "Modern catalytic methods for organic synthesis with diazo compounds", M. P. Doyle, M. A. McKervey and T. Ye, Wiley, 1998.

Examples of rhodium catalyzed intramolecular CH insertion

sp^3 centers: CH bonds adjacent to heteroatoms are activated to attack; *e.g.*

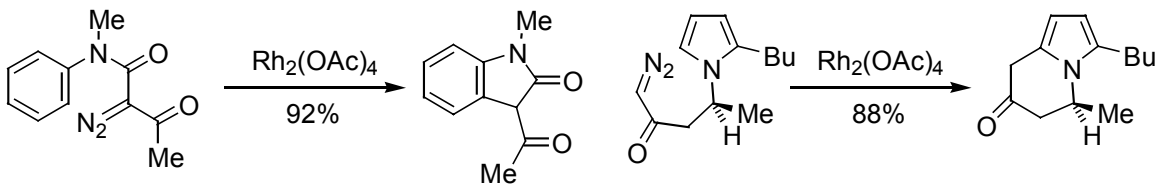


92TL1143



75CC846

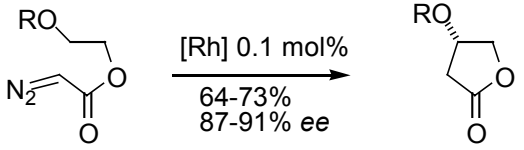
sp^2 centers: best with electron rich aromatics and heteroaromatics; *e.g.*



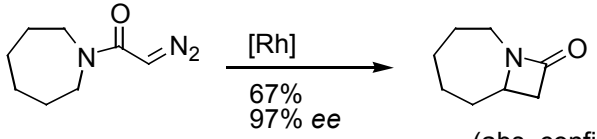
88JOC1017

89HCA1749

Rhodium catalyzed intramolecular CH insertion: Enantioselective reactions induced by chiral catalysts

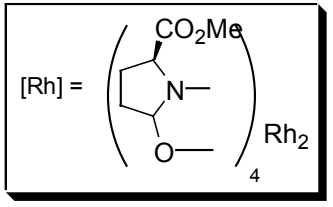


Doyle et al. 91JA8982



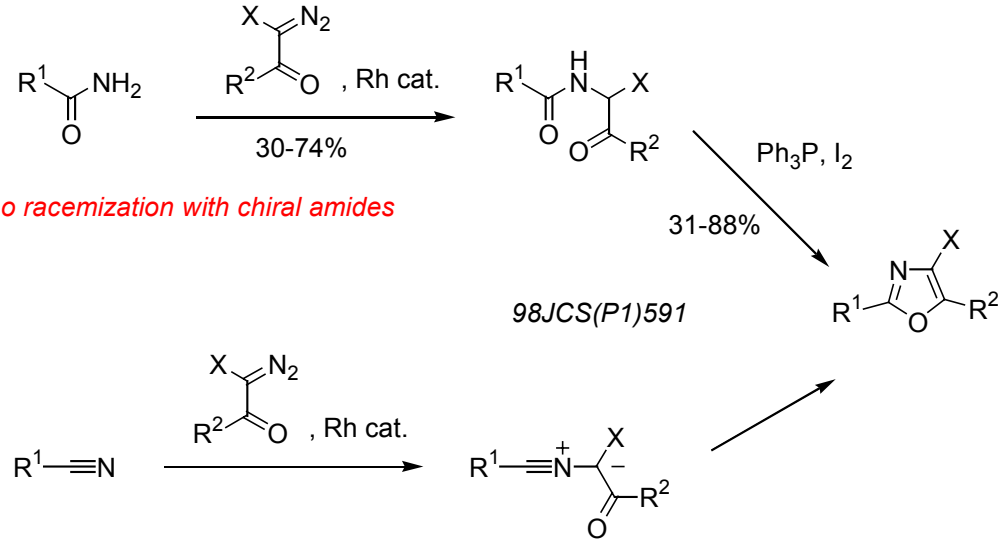
Doyle, Kalinin, 95SL1075

(abs. configuration not specified)



Review: Doyle, Forbes, 98CRV911

Rhodium catalyzed NH insertion and ylide formation as routes to oxazoles

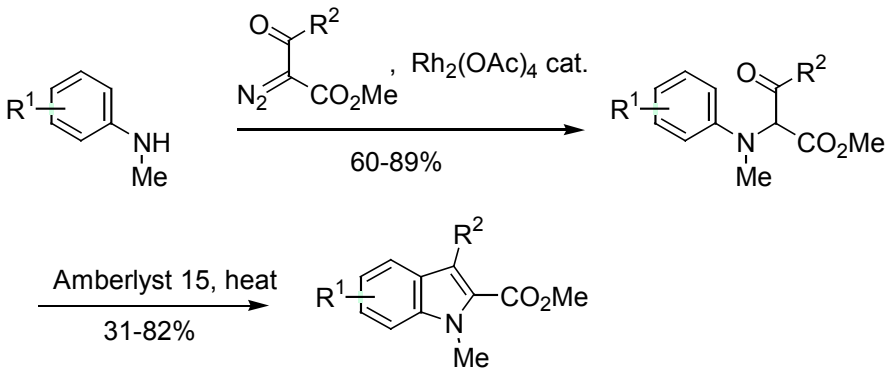


no racemization with chiral amides

98JCS(P1)591

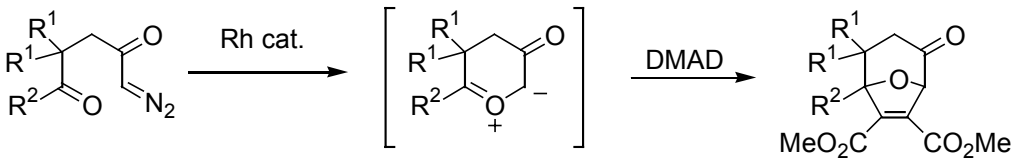
Review: Moody, Doyle, Prog. Heterocycl. Chem., 1998 9, 1.

Rhodium catalyzed intramolecular NH insertion: Application to indole synthesis



Moody, Swann, 98SL135

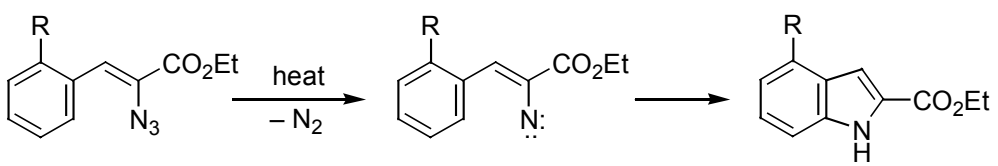
Generation and trapping of carbonyl ylides



For examples with a chiral Rh catalyst leading to asymmetric synthesis see 99JA1417

Nitrene cyclization

This is much less common than carbenoid cyclization: no stabilized "nitrenoids" equivalent to rhodium carbenoids are known. However there are a few useful reactions. The conversion of 2-azidobiphenyl into carbazole is the best known; the following indole synthesis is also valuable.

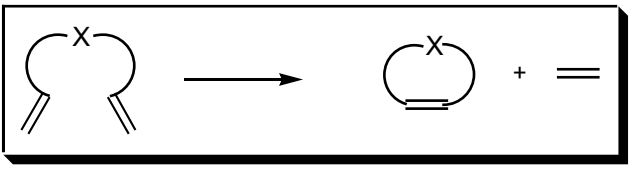


(Hemetsberger indole synthesis)

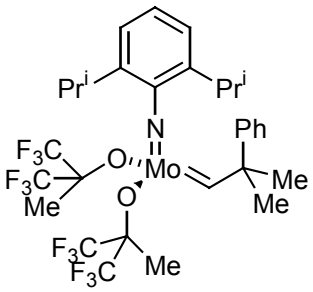
Reviews: Gribble, 00JCS(P1)1045; Contemp. Org. Synth., 1994, 1, 145

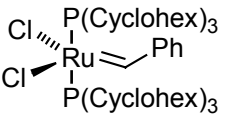
Other examples of nitrene cyclization are in the review by Scriven and Turnbull, 88CRV297

Ring-closing metathesis (RCM) for heterocyclic synthesis



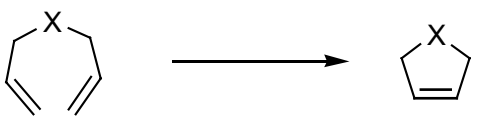
Catalysts must be long lived and tolerant of functional groups, *e.g.*





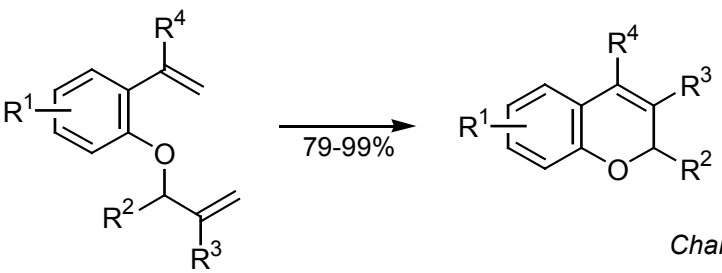
Reviews: Grubbs and Chang, 98T4413;
Phillips and Abell, Aldrichimica Acta, 1999, 32, 75

Ring-closing metathesis: Examples

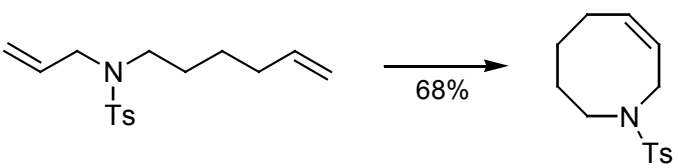


X = S O NH
99 99 82 %

Shon, Lee, 97TL1283

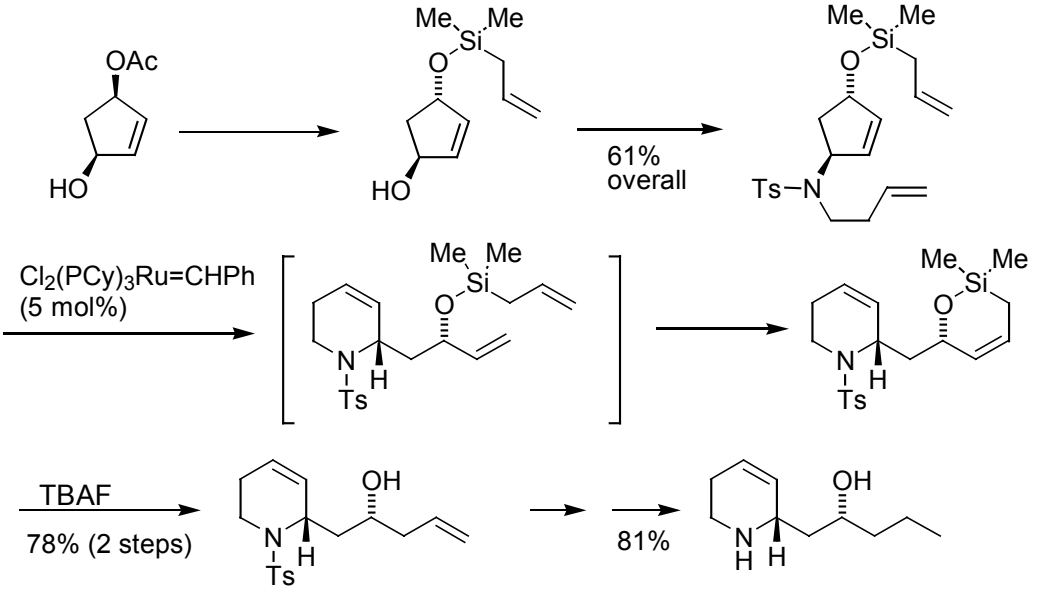


Chang, Grubbs, 98JOC864



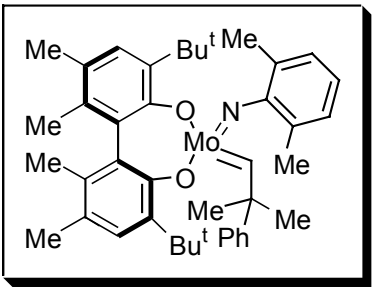
Hoveyda et al., 96JA4291, 97JA6205

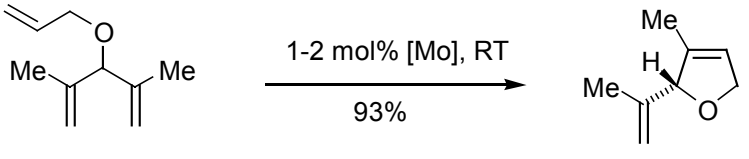
Ring opening metathesis combined with ring closing metathesis: Synthesis of a piperidine alkaloid, (-)-halosaline



Stragies, Blechert, 99T8179

Asymmetric ring closing metathesis

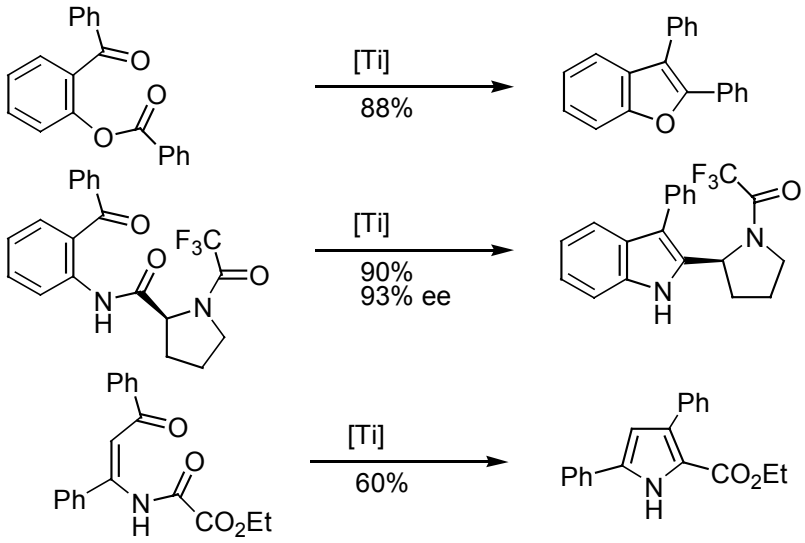




99% ee

Schrock, 99T8141

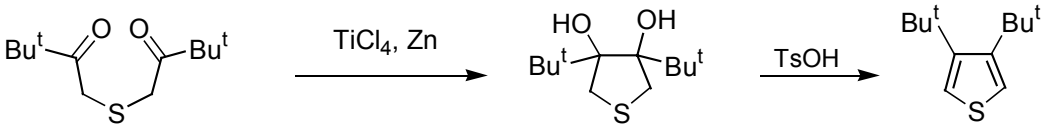
Intramolecular McMurry coupling of carbonyl compounds



[Ti] is " low valent titanium"; *e.g.*, $TiCl_3$ + Zn *in situ*.

Review: 96AG(E)2443

Thiophenes by McMurry type coupling



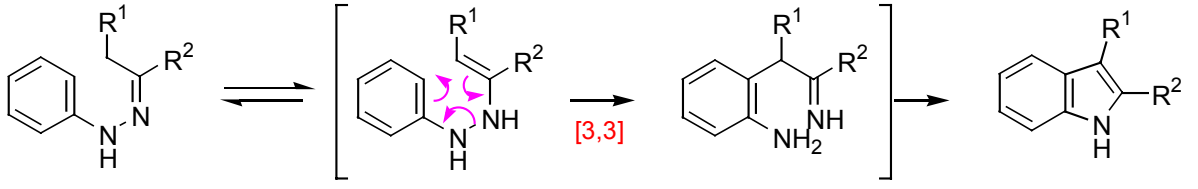
98JOC4912

Rearrangement followed by cyclization

The Fischer indole synthesis and related reactions

The Fischer indole synthesis is still one of the most important and most versatile methods for preparing indoles. The key step is a rearrangement that can be regarded as a [3,3] sigmatropic shift. Several related preparations of indoles are known that appear to be mechanistically related. Some other heterocycles have also been prepared by related methods.

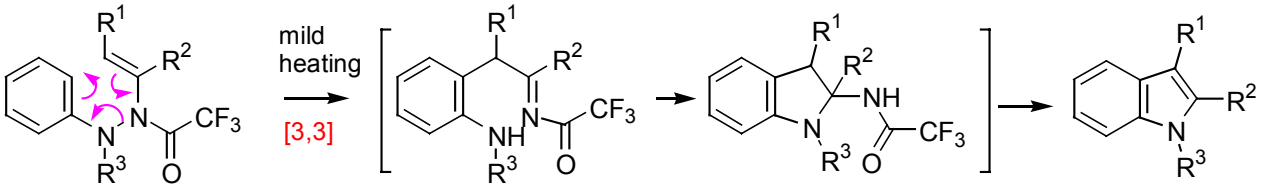
Fischer indole synthesis



An acid or Lewis acid catalyst is usually used so the intermediates may be protonated

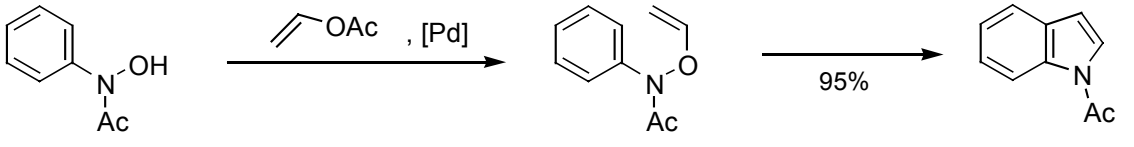
Some recent examples/modifications: 90ACS614, 91JOC3001, 93OPP(25)609, 94JOC3738, 97T8853, 98T45

A related enehydrazine rearrangement/cyclization



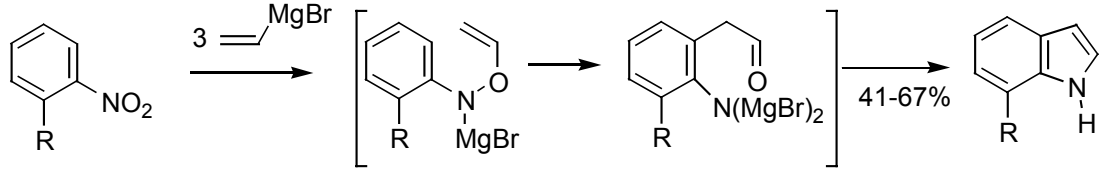
99TL3601

Martin indole synthesis



84HCA1647, 87TL1645

Bartoli indole synthesis

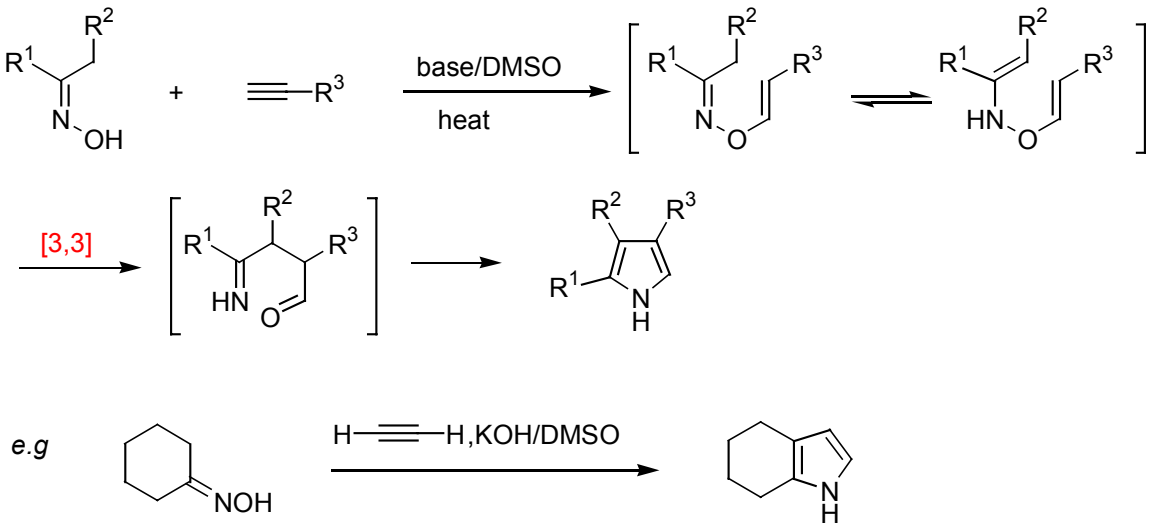


possible intermediates

89TL2129, 91JCS(P1)2757, 92SL79, 98JCS(P1)1193

These indole syntheses are reviewed by Gribble, 00JCS(P1)1045

Trofimov pyrrole synthesis

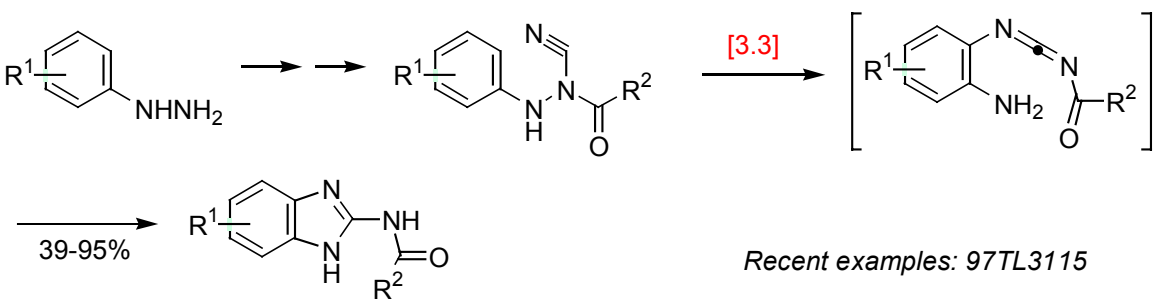


e.g

Reviews: 90AHC(51)178, 98 Russ. J. Org. Chem. 967

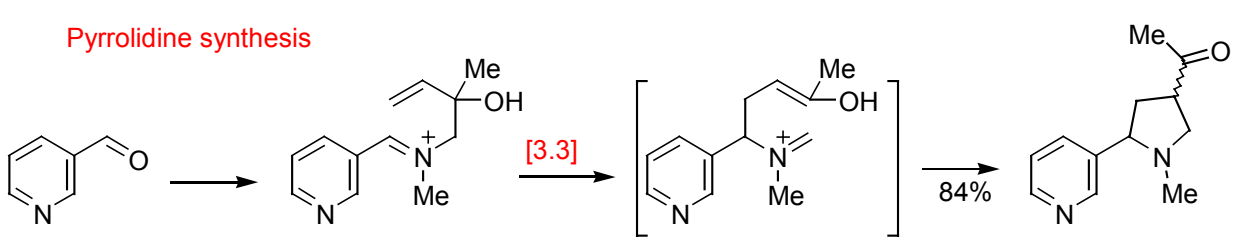
Some other syntheses involving [3,3] shifts

Pellizzari benzimidazole synthesis



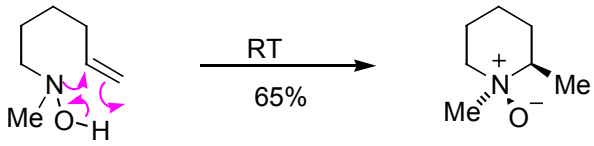
Recent examples: 97TL3115

Pyrrolidine synthesis

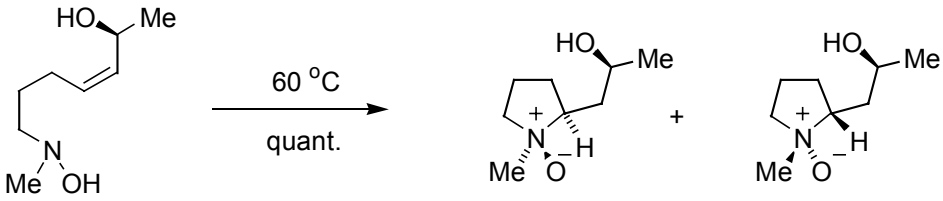


79JA1310, 79TL4041

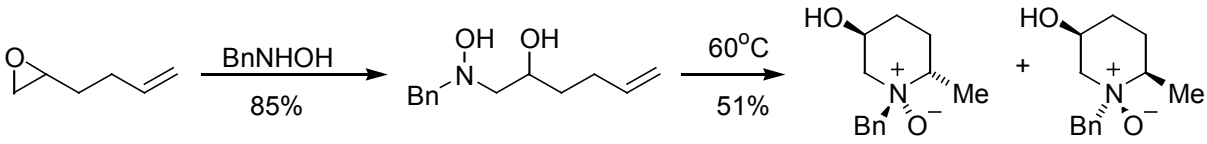
The "reverse Cope" cyclization



85JOC5795, 95JOC5803



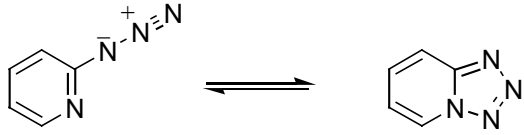
99TL5915

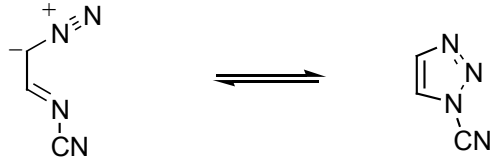


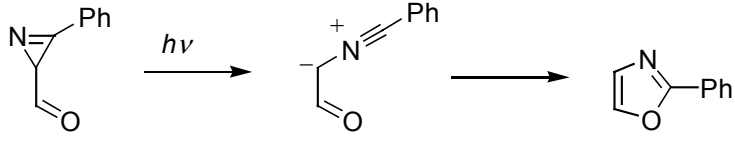
98TL9089

Electrocyclic reactions: Formation of five-membered rings

("1,5-Dipolar cyclization reactions")

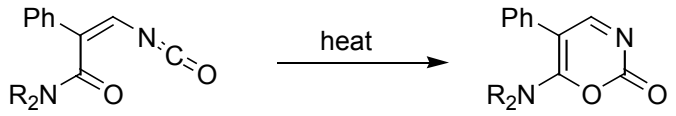


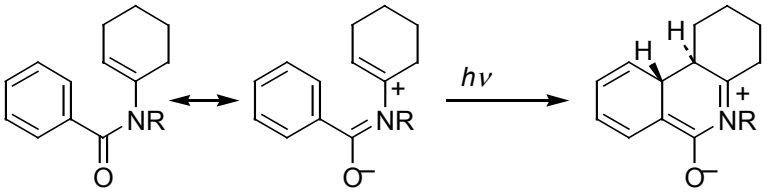




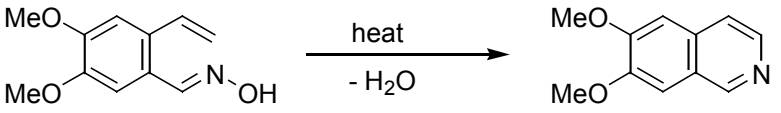
Reviews: 80AG(E)947; 79CRV181

Electrocyclic reactions: Formation of six-membered rings





80JCSP(1)197

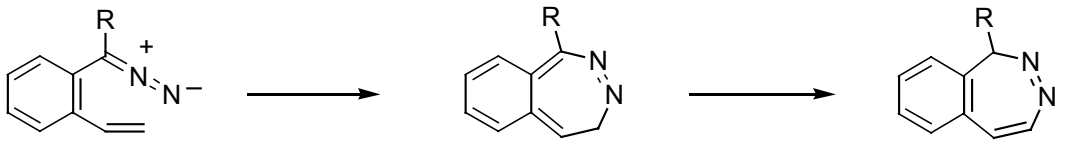


89H (28)275, 88JCSP(1)2429

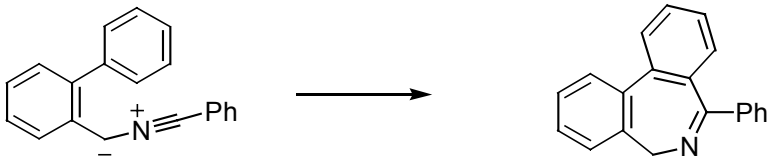
Review: Marvell, "Thermal Electrocyclic Reactions", Academic Press, 1980.
Some more recent examples: 95T9119, 98TL1995, 98TL2341

Electrocyclic reactions: Formation of seven-membered rings

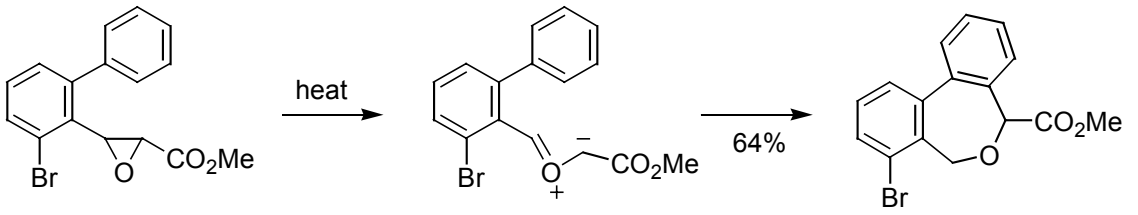
("1,7-Dipolar cyclization reactions")



Review: Zecchi, 91S181



91CC658



97JCS(P1)3025

2 Cycloaddition methods

A cycloaddition reaction can be defined as one in which a ring system is constructed by the formation of two new bonds with no small molecules (such as nitrogen or carbon dioxide) being eliminated in the process. Some of these reactions are described as concerted since the two new bonds are formed without any reaction intermediates. In other formal cycloadditions, intermediates (either charged or radical species) can be shown to be involved and the cycloaddition process is therefore stepwise. In reactions of this second type there is no clear boundary between cycloaddition and cyclization processes. Nevertheless the following general types of heterocyclic ring forming reactions are commonly classified as cycloadditions.

- 1,3-Dipolar cycloadditions
- Hetero Diels–Alder reactions
- [2 + 2] cycloadditions

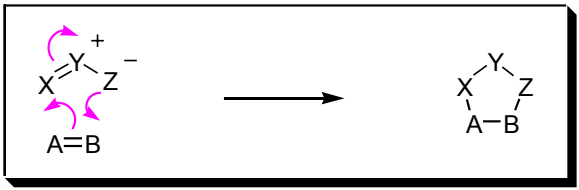
These result in the formation of heterocycles containing 5, 6 and 4 atoms, respectively. They are presented in this order because it reflects their relative importance. There are a few other cycloaddition reactions that lead to heterocycles with 3 or 7 atoms, and some examples of these are also given.

1,3-Dipolar cycloaddition

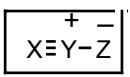
1,3-Dipoles are so called because it is not possible to write valence bond structures for them without including formal positive and negative charges. This does not imply that 1,3-dipoles are highly polar species: most are not. Many, but not all, 1,3-dipoles will participate in cycloaddition reactions with partners that have double or triple bonds (so-called dipolarophiles). These reactions are an important method of synthesis of a wide variety of five membered heterocycles.

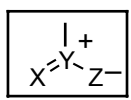
Some 1,3-dipoles, such as azides and nitrones, are isolable species but the majority of 1,3-dipoles are transient intermediates that are usually generated in the cycloaddition process. There are two general types of 1,3-dipole: those in which a resonance form containing a formal triple bond can be written (with the central atom sp hybridized), and those in which the central atom is sp^2 hybridized.

1,3-Dipolar cycloaddition: some general considerations



1,3-Dipoles that are useful in cycloaddition reactions





azides

diazo compounds

nitrile oxides

nitrile imides

nitrile sulfides

nitrile ylides

nitrones

azomethine imides

azomethine ylides

carbonyl ylides

thiocarbonyl ylides

Reactivity toward dipolarophiles may be modest, leading to low overall yields of adducts, especially with transient 1,3-dipoles

Regioselectivity of cycloaddition is sometimes poor

Stereoisomeric mixtures can result from cycloadditions of nitrones and similar dipoles with central sp^2 hybridization.

Some possible solutions:

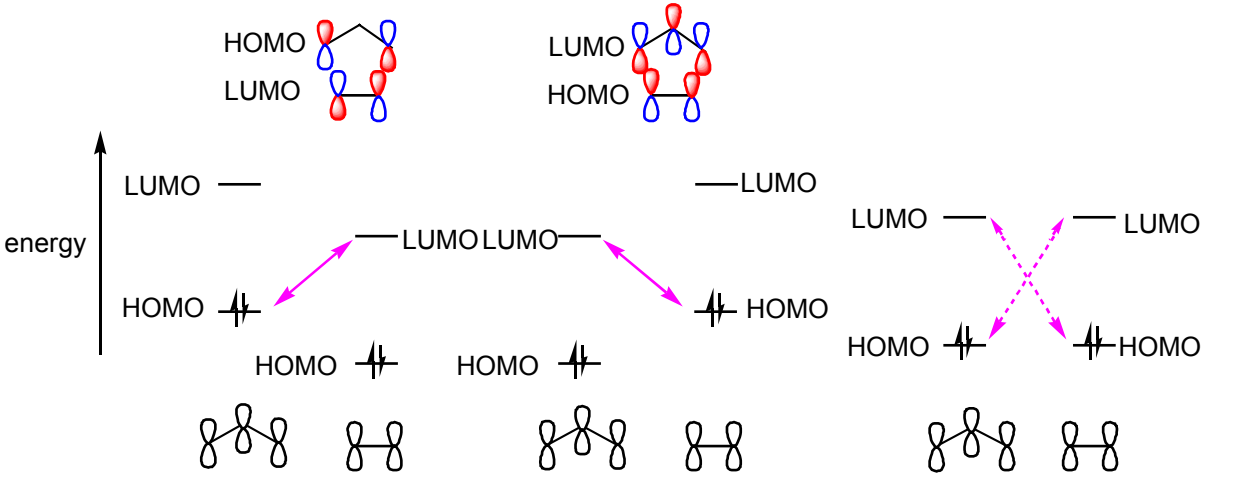
Theory (especially frontier orbital theory) can help to predict reactivity and regioselectivity of various potential dipole-dipolarophile combinations

Intramolecular dipolar additions can overcome some reactivity and selectivity problems

Stable versions of transient dipoles (such as mesoionic compounds) can help to solve reactivity problems

Lewis acid catalysts may improve reactivity and regioselectivity in some cases

Frontier orbital interactions in 1,3-dipolar cycloaddition



Type (i): dominant interaction is HOMO dipole-LUMO dipolarophile

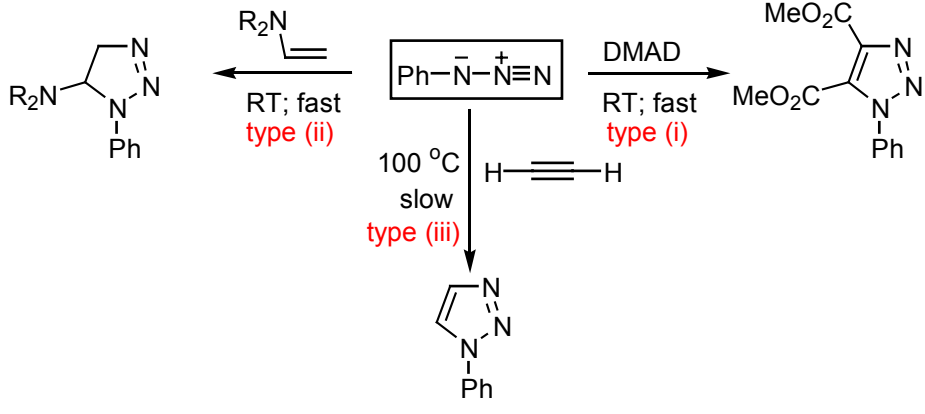
Type (ii): dominant interaction is LUMO dipole-HOMO dipolarophile

Type (iii): no dominant interaction

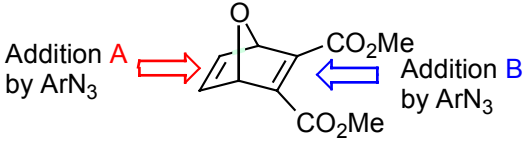
Reactivity in 1,3-dipolar cycloaddition

Most 1,3-dipoles are of type (i) so react best with electron deficient dipolarophiles.

Many dipoles can also react by type (ii) interactions if the dipolarophile is strongly electron donating: *e.g.*



Substituents on the dipole can have a strong influence: *e.g.*

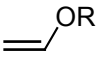


Ar	Ratio A:B
Ph	17:83
4-MeO.C_6H_4	9:91
4-NO_2.C_6H_4	49:51

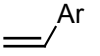
81T1349

Analysis of reactivity

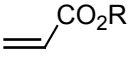
Dipolarophile



LUMO +3 eV
HOMO -8 ev

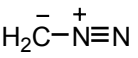


LUMO +1 eV
HOMO -9 ev



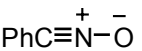
LUMO 0 eV
HOMO -11 ev

Dipole



LUMO +1.8 eV
HOMO -9 ev

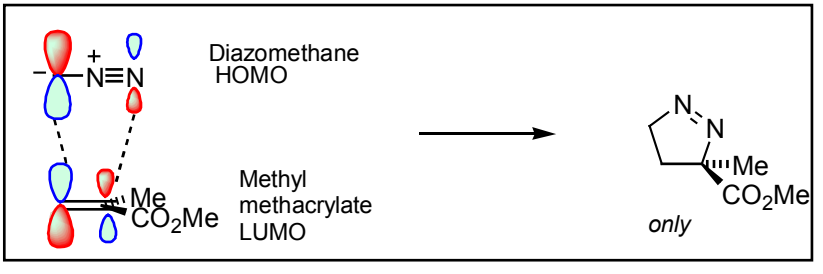
Enol ethers: slow addition
Acrylates: fast addition; HOMO dipole controlled



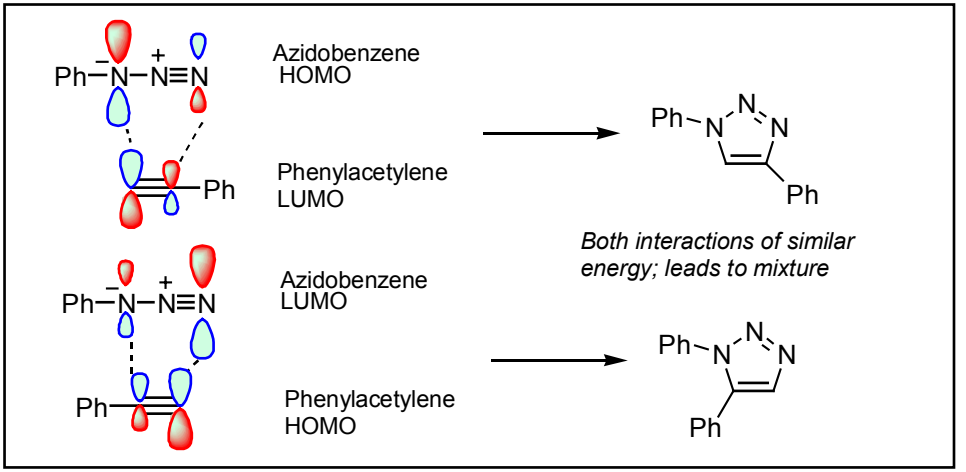
LUMO -1 eV
HOMO -10 ev

Enol ethers: fast addition; LUMO dipole controlled
Acrylates: both interactions important

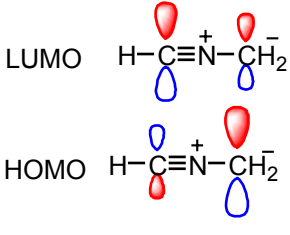
Analysis of regioselectivity

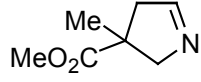


Regioselectivity is determined by combination of the orbitals in the energetically more favourable orientation: orbitals with larger coefficienets interact

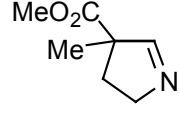


***Problem*: Orbital coefficients for the HOMO and LUMO of the nitrile ylide $HCNCH_2$ are shown. Assume that the dipole reacts with methyl methacrylate in a type (i) process and predict the likely major reaction product, A or B.**



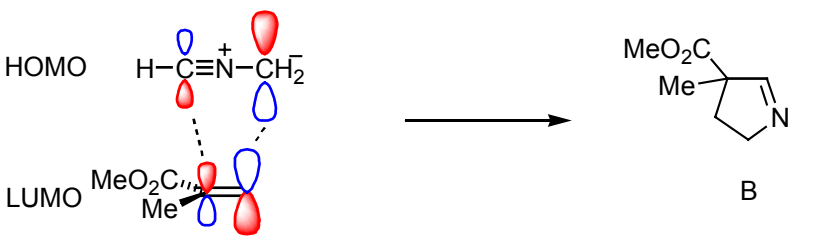


A

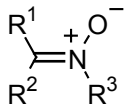


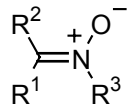
B

***Answer*: The reaction is controlled by the HOMO of the dipole and the LUMO of methyl methacrylate. So the preferred regioselectivity is determined by combining the larger coefficients on each of the appropriate orbitals:**



Selectivity problems illustrated: nitrones + alkenes



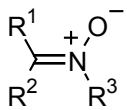


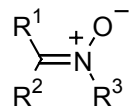
E/*Z* isomers possible; may interconvert or may be formed as a mixture (not a problem with cyclic nitrones)

endo vs.

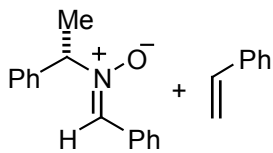
exo selectivity

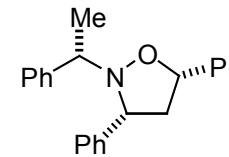
regioselectivity





Selectivity in cycloaddition of a chiral nitrone

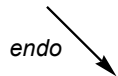


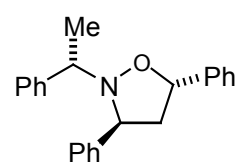


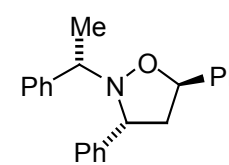
11

76

90% total







5

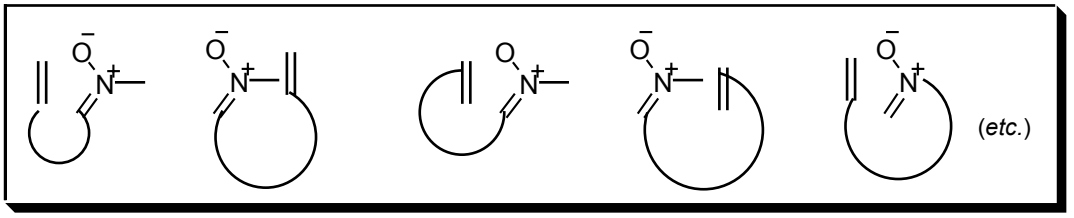
8

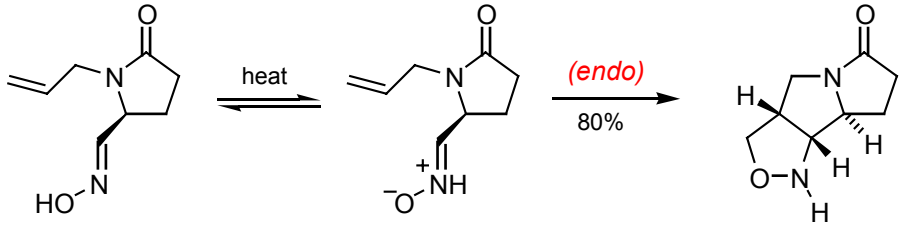
But note that even though the addition is completelyregioselective there are still 4 isomers

Belzecki, Panfil, 79JOC1212

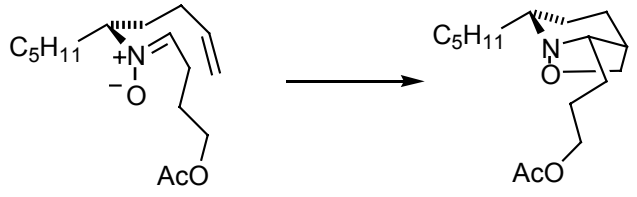
Review of asymmetric 1,3-dipolar addition: Gothelf, Jørgensen, 98CRV863

Intramolecular dipolar addition: nitrones





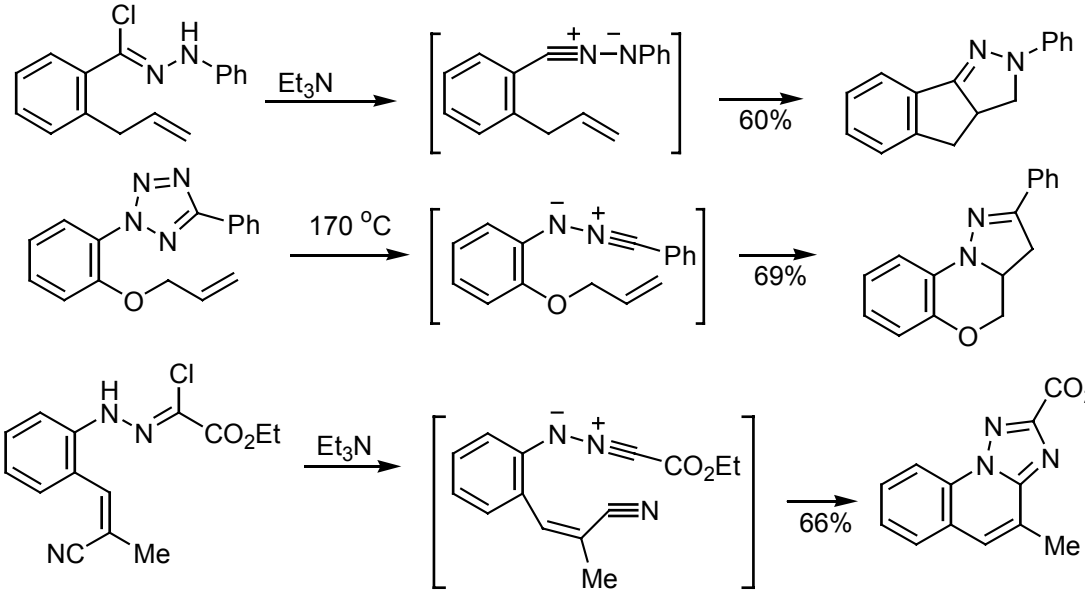
Hassner et al., 94TL2397



Holmes et al., 88JA8696

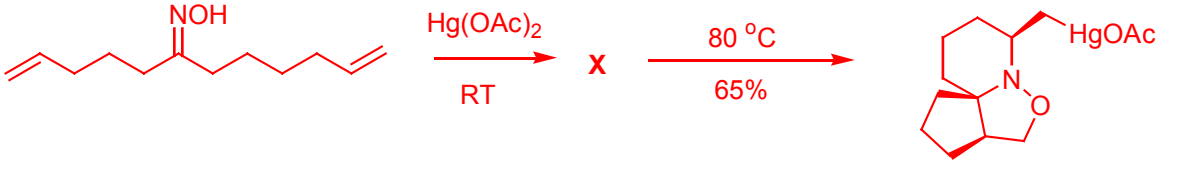
(Intramolecular addition often reduces the number of possible isomers)

Intramolecular dipolar additions of nitrile imides

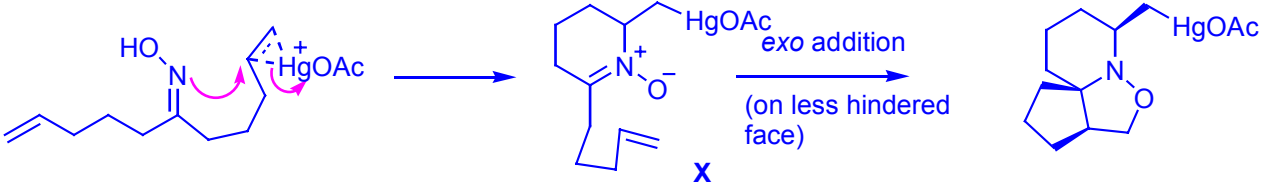


Review: Zecchi et al., 98H(47)541

***Problem*: Identify the intermediate X and explain the reactions involved in the following transformation:**



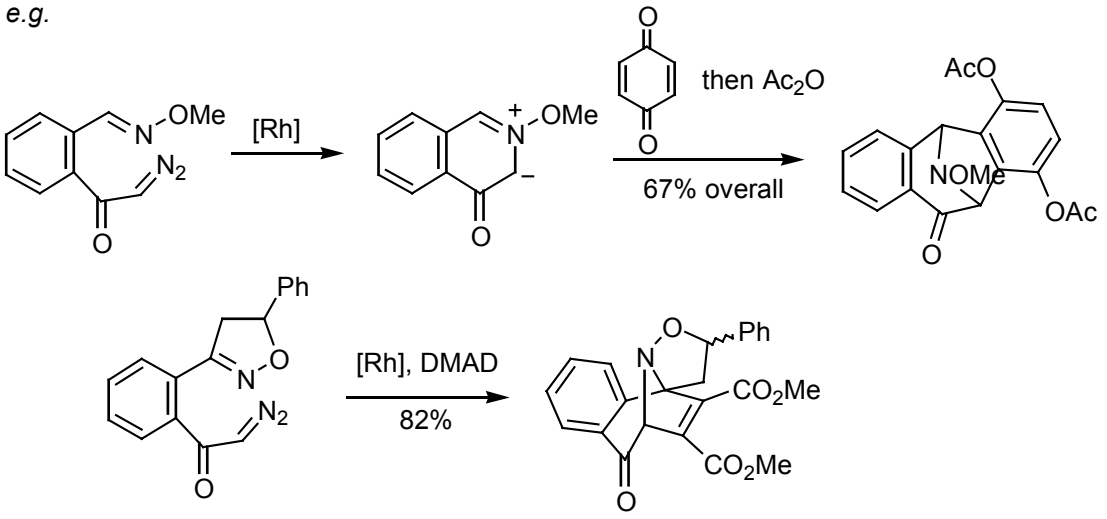
***Answer*: The formation of X is a mercury(II) catalyzed 6-*exo* cyclization in which the nitrogen atom of the oxime acts as a nucleophile. This produces the nitrone X which is then set up for an intramolecular 1,3-dipolar addition (*exo* transition state). The regiochemistry and stereochemistry are probably determined by steric factors.**



92CC1388

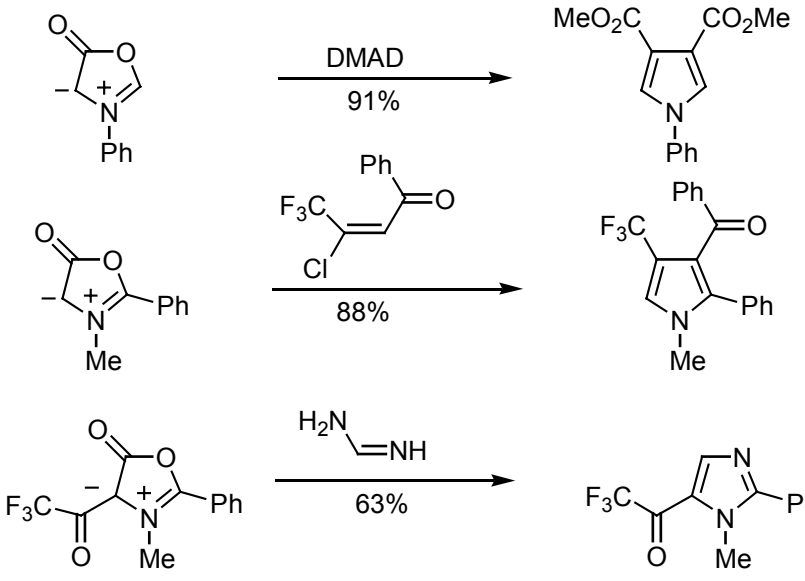
Cyclic azomethine ylides from diazocarbonyl compounds

e.g.



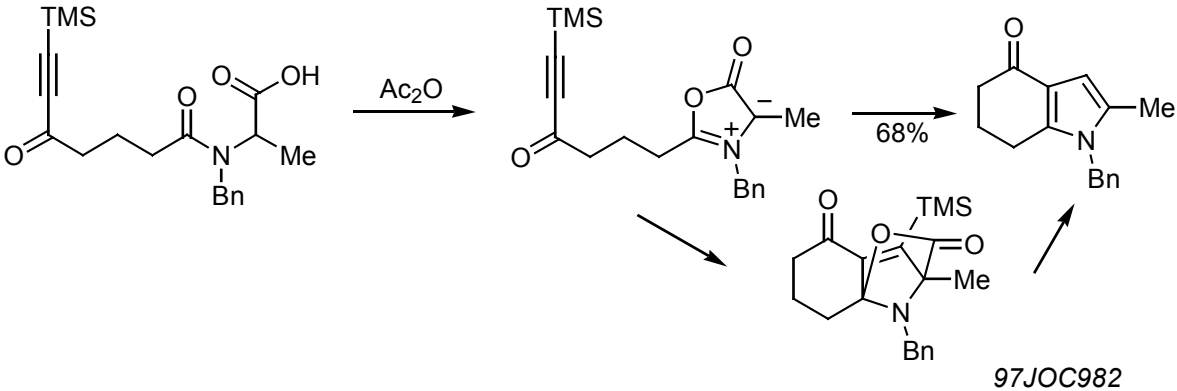
Review: Padwa, Weingarten, 96CRV223

Mesoionic 1,3-oxazolium-5-olates (Münchnones): stabilized azomethine ylides

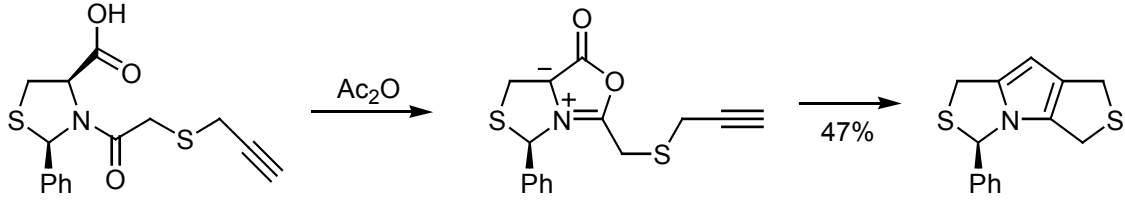


Since azomethine ylides are usually transient, such mesoionic compounds provide a stabilized alternative. Note that the final products are derived by loss of CO_2 from the primary adducts (also NH_3 in the last example).

Intramolecular cycloadditions of Münchnones

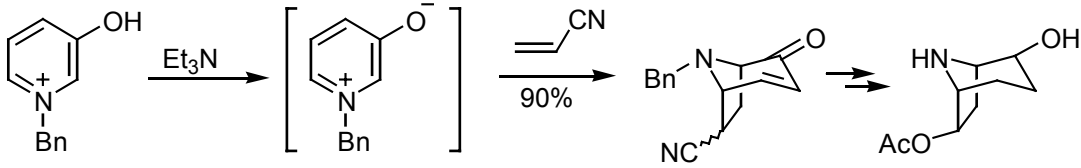


97JOC982

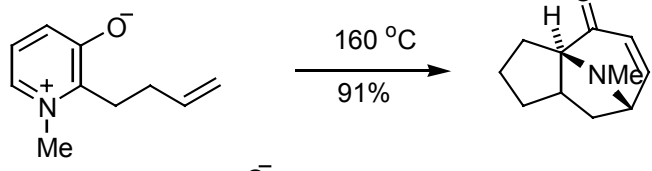


99JCS(P1)1219

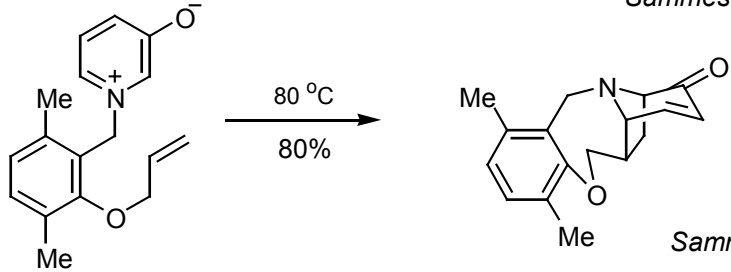
Examples of cycloaddition of oxidopyridiniums



Jung et al., 92JOC3528



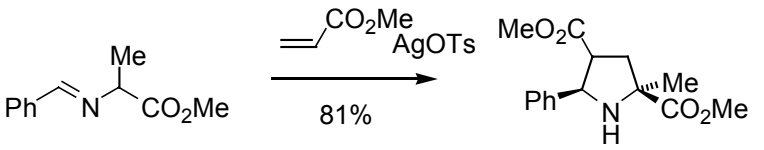
Sammes et al., 90JCS(P1)353



Sammes et al., 93CC607

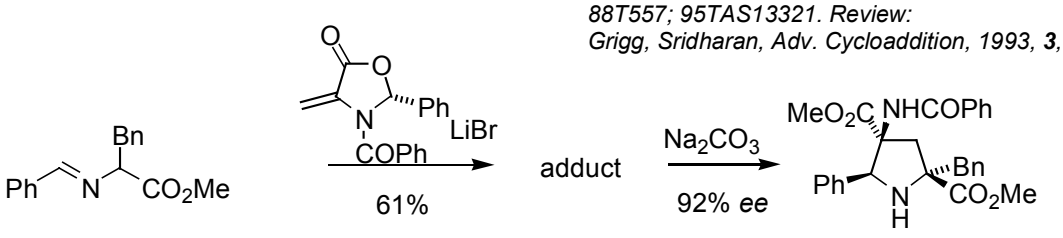
Review: Katritzky, 76AG(E)1

Pyrrolidines from azomethine ylides

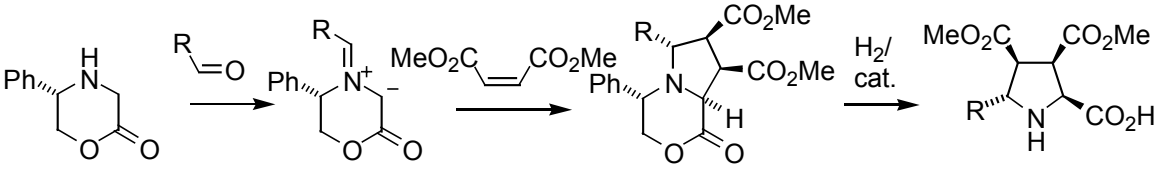


The azomethine ylide is generated from the imine by Ag^+ catalyzed tautomerization.

*88T557; 95TAS13321. Review: Grigg, Sridharan, Adv. Cycloaddition, 1993, **3**, 161.*

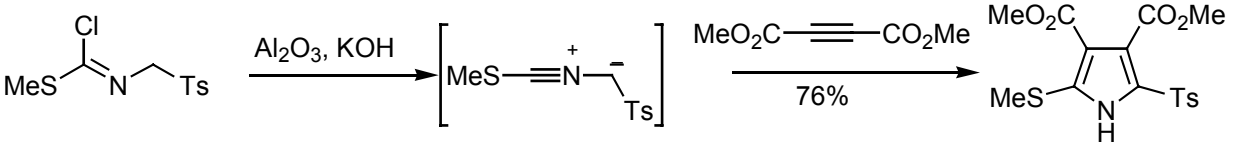


Pyne et al., 95TL2511

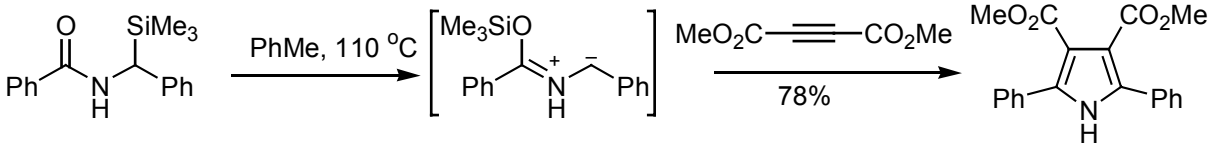


Harwood et al., 95TAS1557

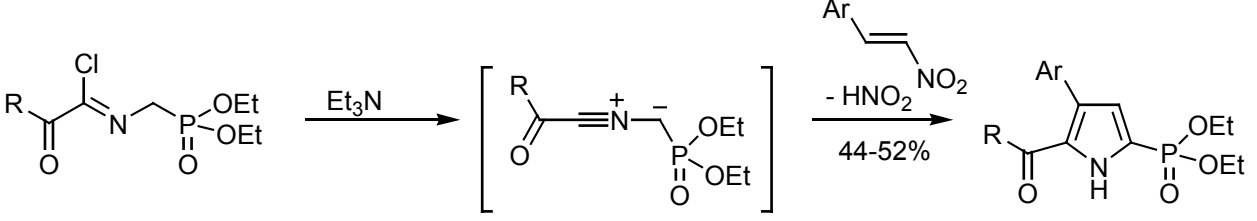
Pyrroles by 1,3-dipolar cycloaddition



92TL6155

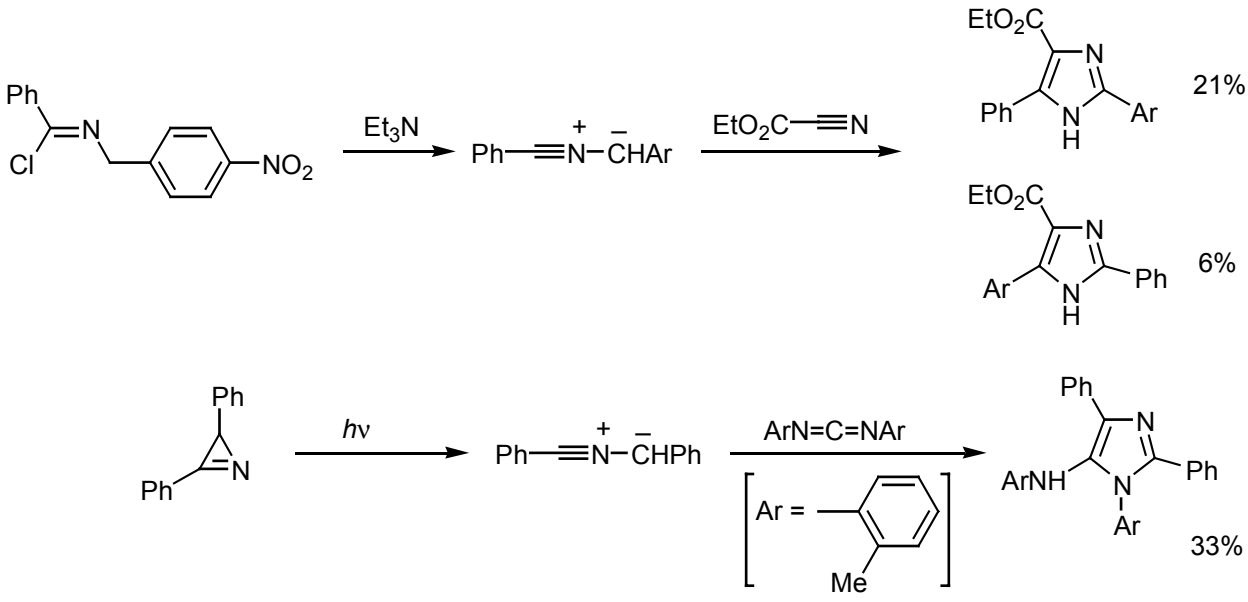


91TL5813



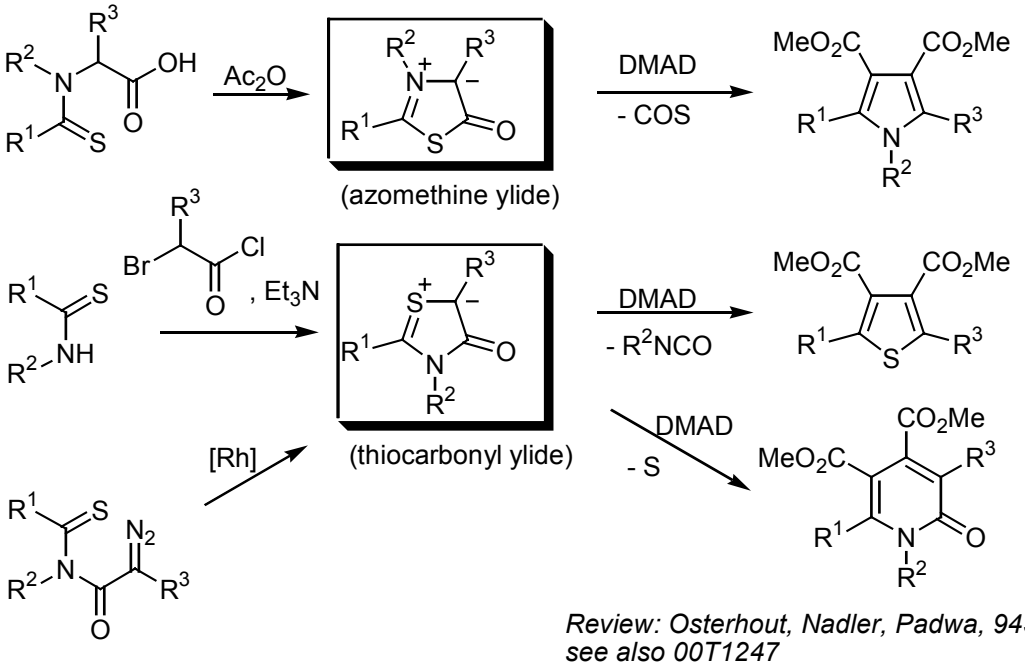
96JCS(P1)1893

Imidazoles by 1,3-dipolar cycloaddition of nitrile ylides



Review: 96CHECII(3)

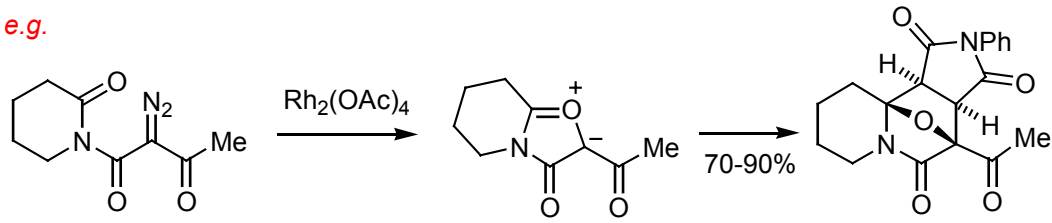
Cycloaddition of sulfur-containing mesoionics



Review: Osterhout, Nadler, Padwa, 94S123; see also 00T1247

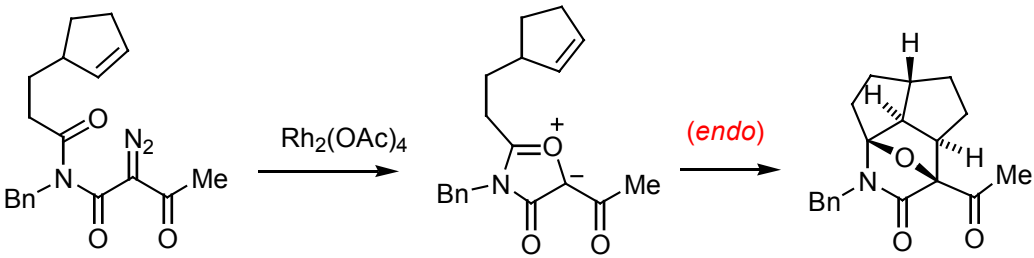
Isomünchnones: cyclic carbonyl ylides

e.g.



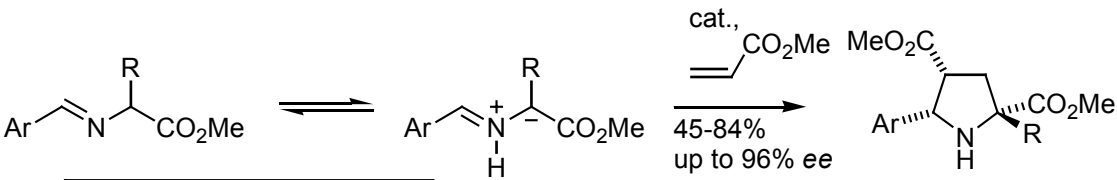
in situ cycloaddition of
N-phenylmaleimide

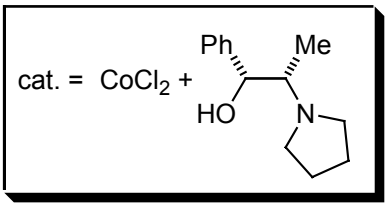
Intramolecular cycloaddition also possible; *e.g.*



Review: Padwa, Weingarten, 96CRV223

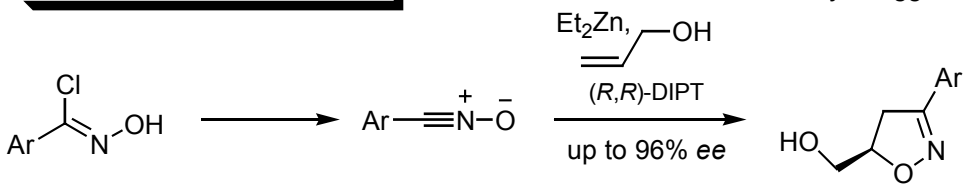
Chiral catalysts for 1,3-dipolar cycloaddition





Ligand occupies two equatorial sites on Co.
Imine bound via N (eq.) and C=O of ester (ax.)
Ph of chiral ligand shields one face of dipole

Allway, Grigg, 91TL5817



DIPT (di-isopropyl tartrate)
can be used in catalytic amounts

Ukaji et al. 93CL1847, 96CL455

Review (nitrones): Gothelf, Jørgensen, 00CC1449

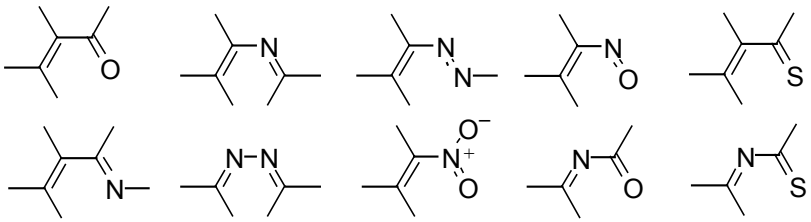
Hetero Diels–Alder reactions

The importance of the Diels–Alder reaction for the construction of six-membered carbon rings is well recognized. The reaction is also an extremely useful method for making six-membered heterocycles. Heteroatoms can be incorporated into either the diene or the dienophile component and most of the mechanistic principles governing the Diels–Alder reaction also apply to its heterocyclic counterpart. In fact the first clear literature example of the Diels–Alder reaction was with a heterodienophile (diethyl azodicarboxylate); see Diels et al., Liebigs Annalen, 1925, 443, 242.

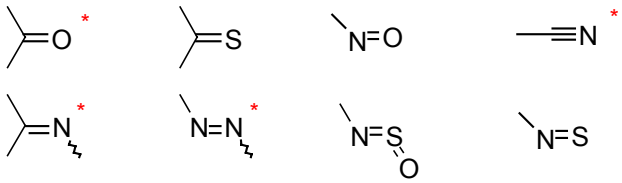
One important difference applies to reactions involving heterodienes. These are sometimes highly electron deficient and so react best with electron rich dienophiles [the equivalent of type (ii) dipolar cycloadditions]. These are sometimes called "inverse electron demand" Diels–Alder reactions.

Reaction partners for the hetero Diels-Alder reaction

Heterodienes



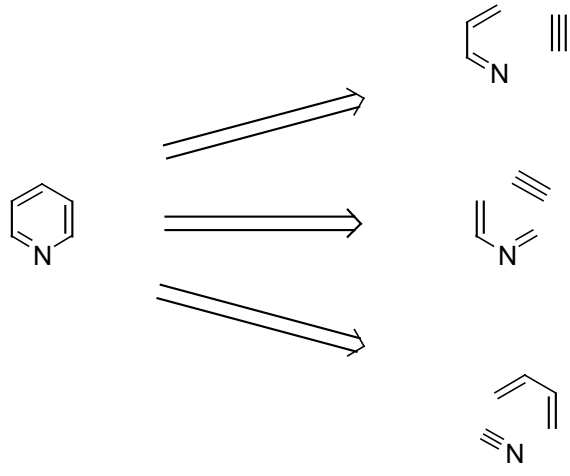
Heterodienophiles



* Usually need activating (electron withdrawing) substituents

Cycloaddition routes to pyridines

To illustrate how the reaction is used to construct heterocycles, three approaches to the pyridine ring system are shown with three different types of hetero Diels-Alder reaction. (An oxidation step would also be needed to produce the fully aromatic ring).



Examples

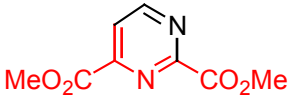
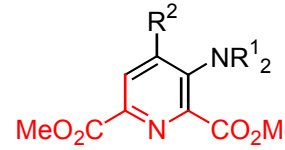
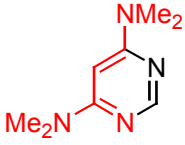
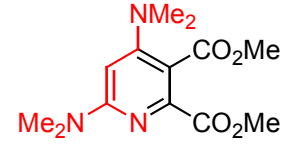
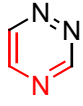
88HCA493

96T10095

95LA1587

The heterodiene components of such reactions are often incorporated into easily accessible heterocycles such as triazines and tetrazines.

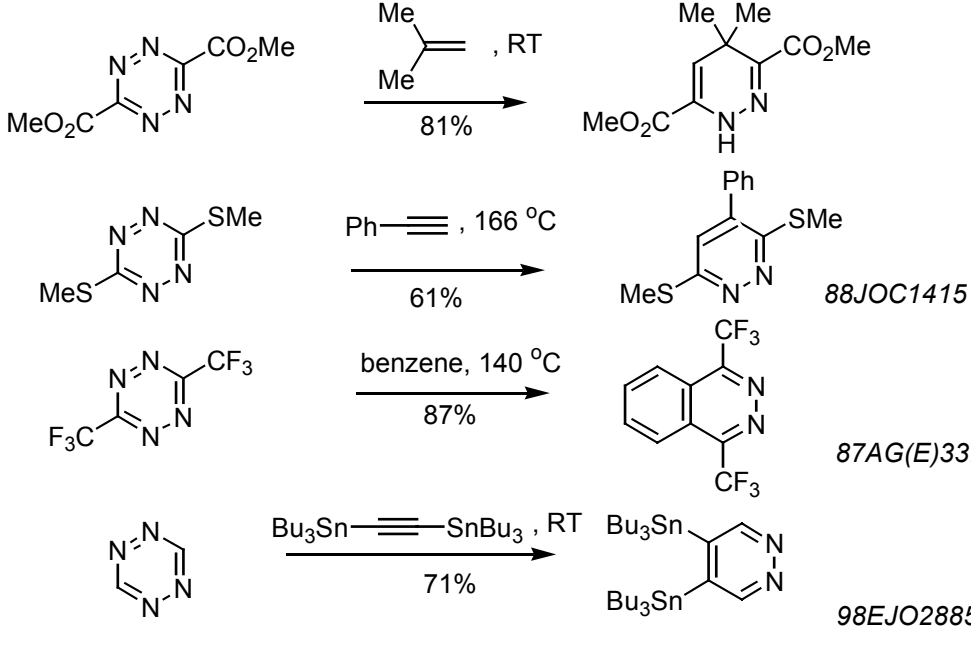
Diazines and triazines as dienes in the Diels–Alder reaction

Diene	*Dienophile type*	*Product*
	electron rich (ynamines, etc.)	
	electron deficient (DMAD. etc.)	
	electron rich (ynamines, etc.)	

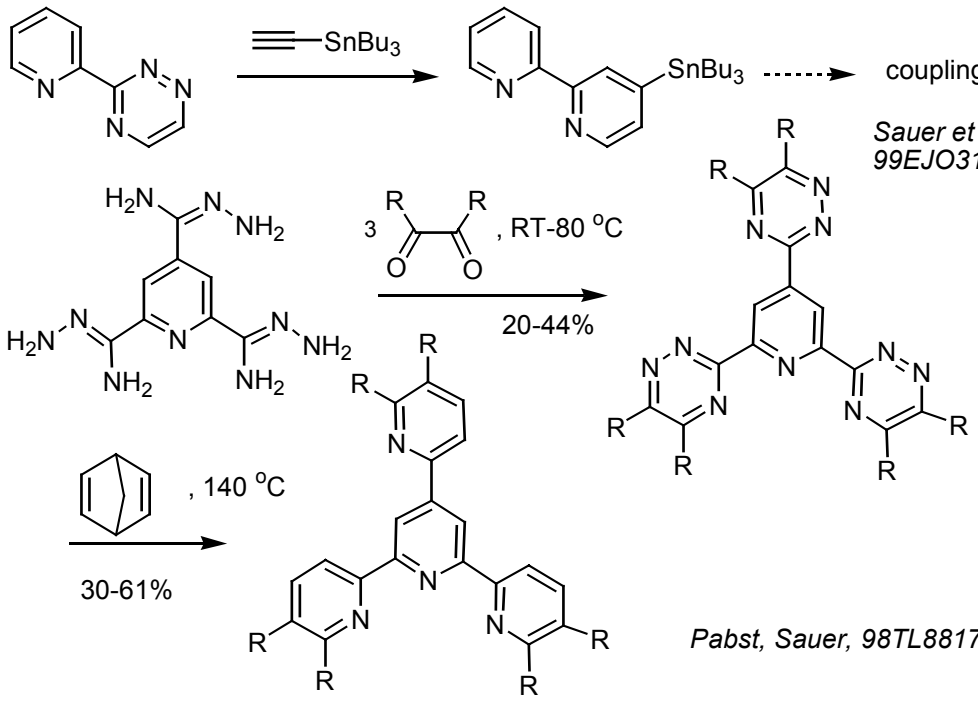
In these reactions a small molecule (HCN or N_2) is lost from the primary Diels-Alder adduct (not isolable).

Review: Boger, 91COS(5)451

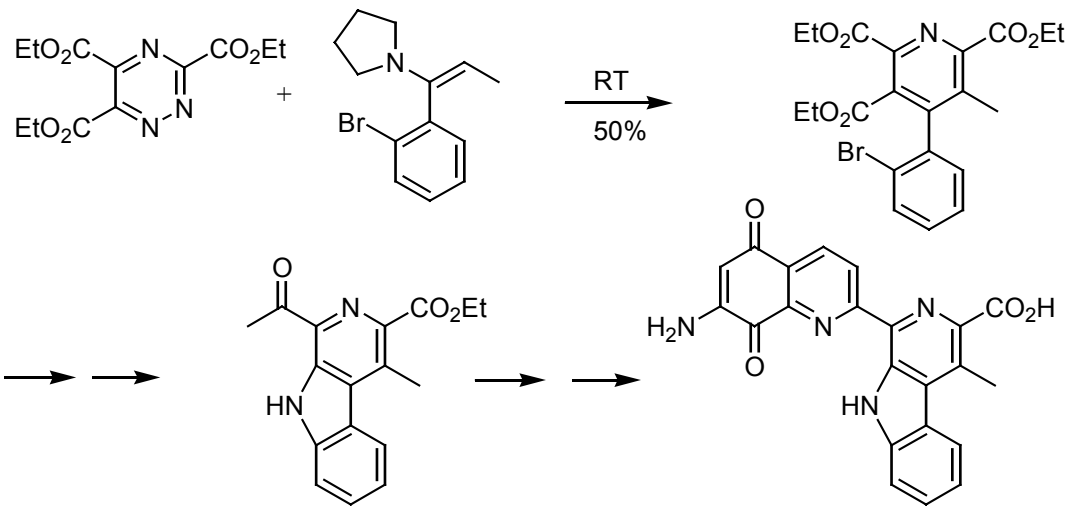
1,2,4,5-Tetrazines as dienes



Sauer's polypyridine synthesis from 1,2,4-triazines

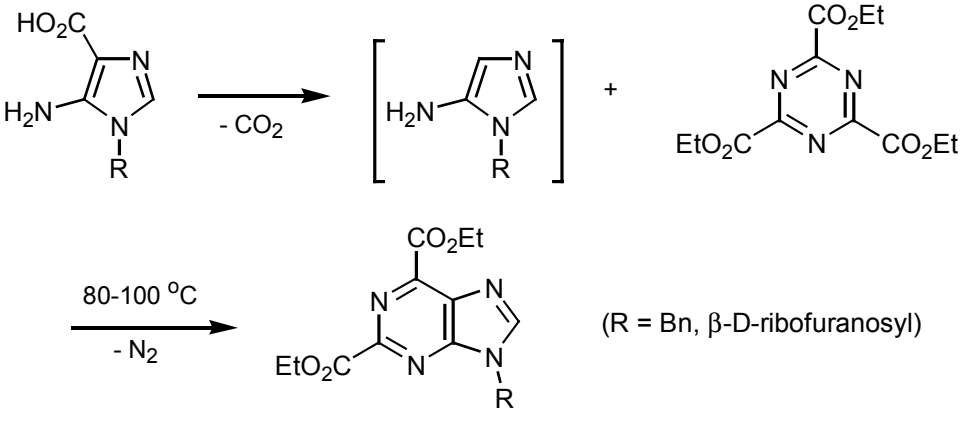


1,2,4-Triazine cycloaddition: Lavendamycin synthesis



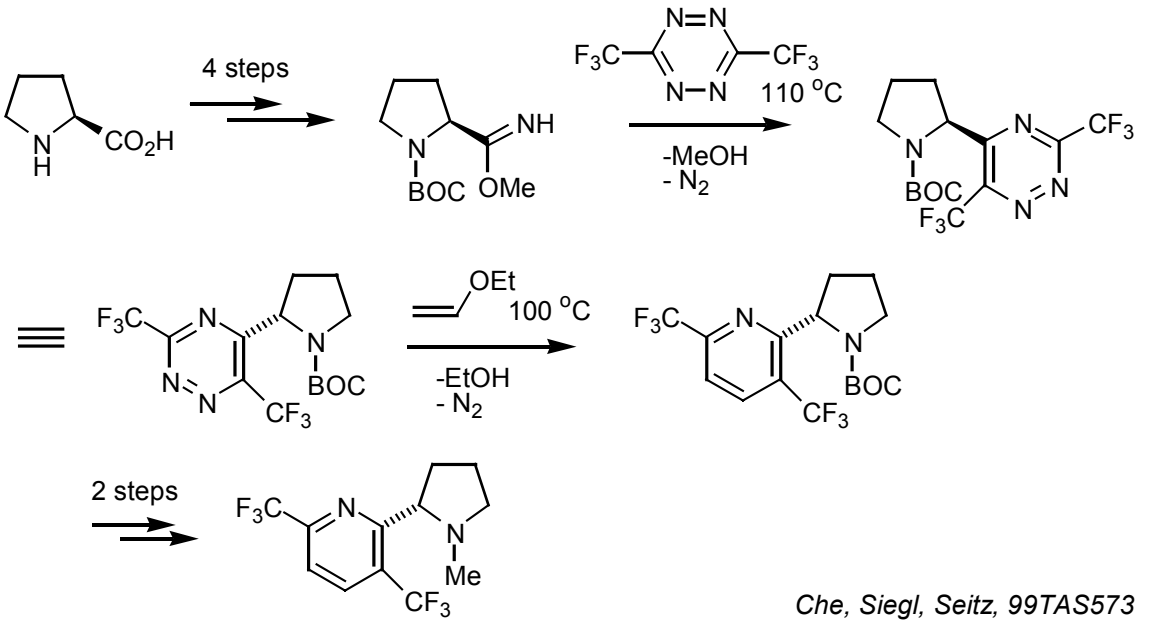
Review: Boger, 91COS(5)451

A purine synthesis by inverse demand Diels-Alder reaction



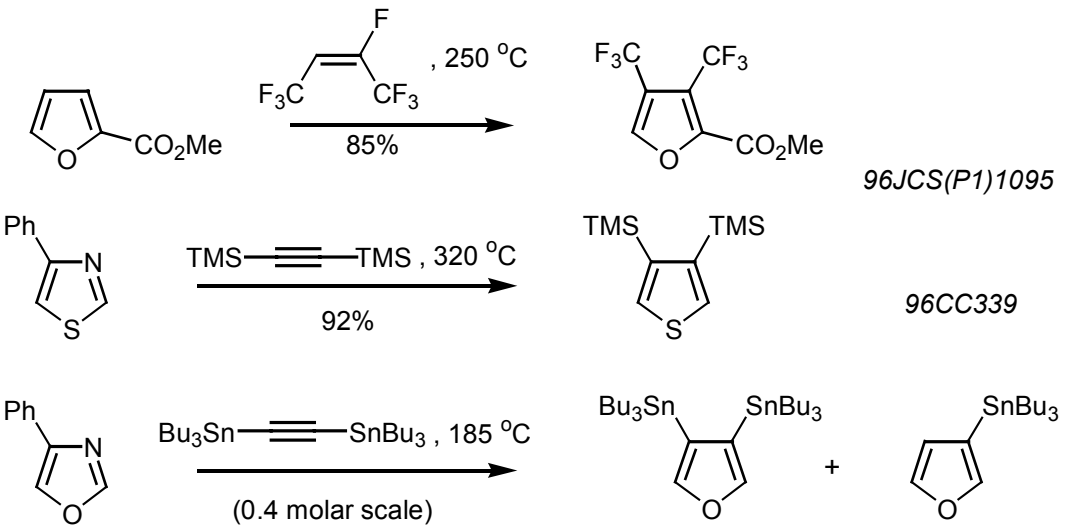
Dang, Liu, Erion, 99JA5833

A nicotine analogue by inverse demand Diels-Alder reactions



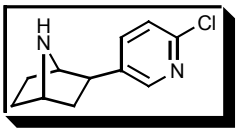
Che, Siegl, Seitz, 99TAS573

Other Diels–Alder – retro Diels–Alder syntheses



Notice that even these normally unreactive heterocycles and dienophiles will react under forcing conditions.

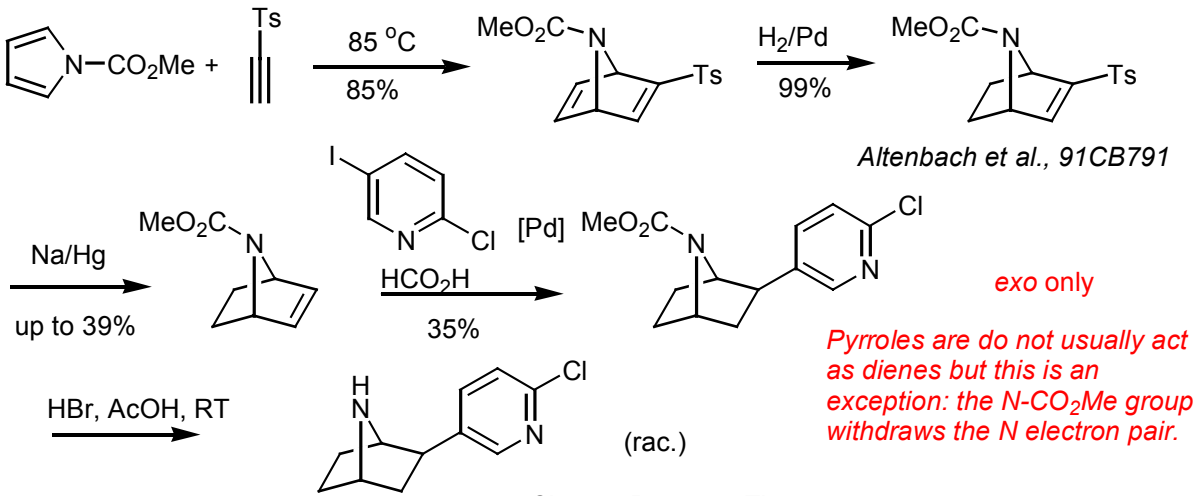
General review on furan synthesis: Wong et. al., 98T1955

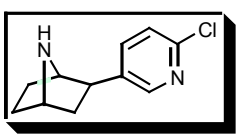


Epibatidine by Diels-Alder addition to pyrroles

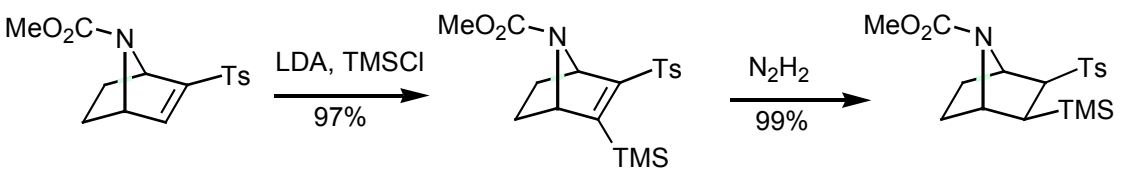
Some problems:

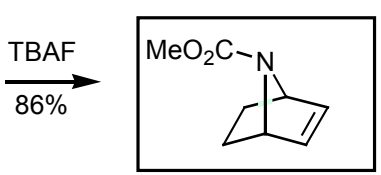
How to find sufficiently reactive partners?
How/when to introduce the chloropyridyl group?
How to achieve an asymmetric synthesis?





Some modifications and improvements to the route



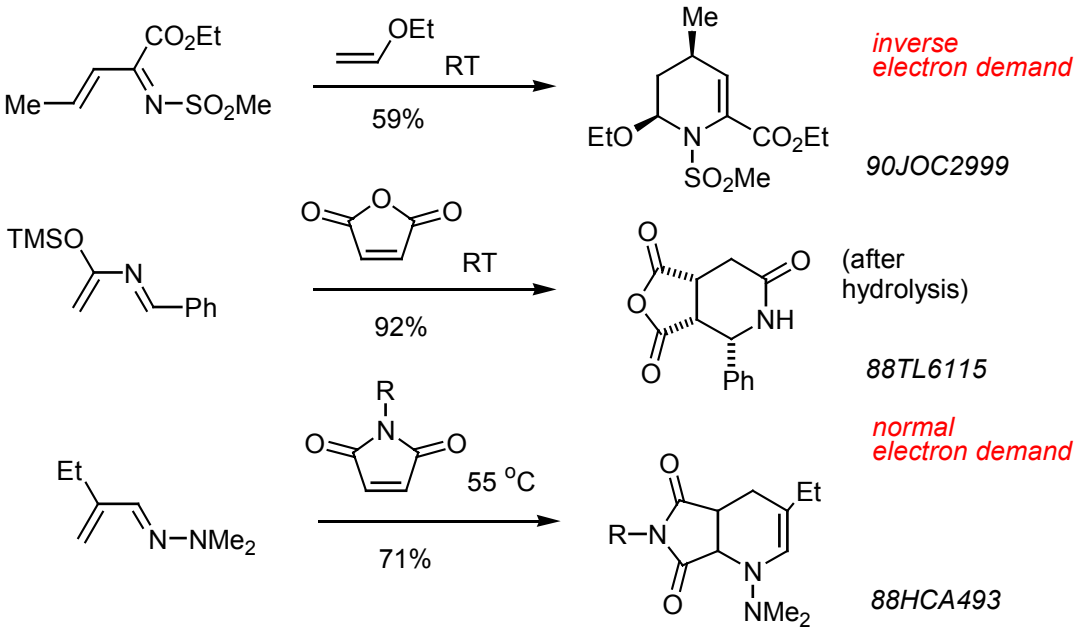


better yields in later steps → *Otten, Kaufmann et al., 98EJOC1997*

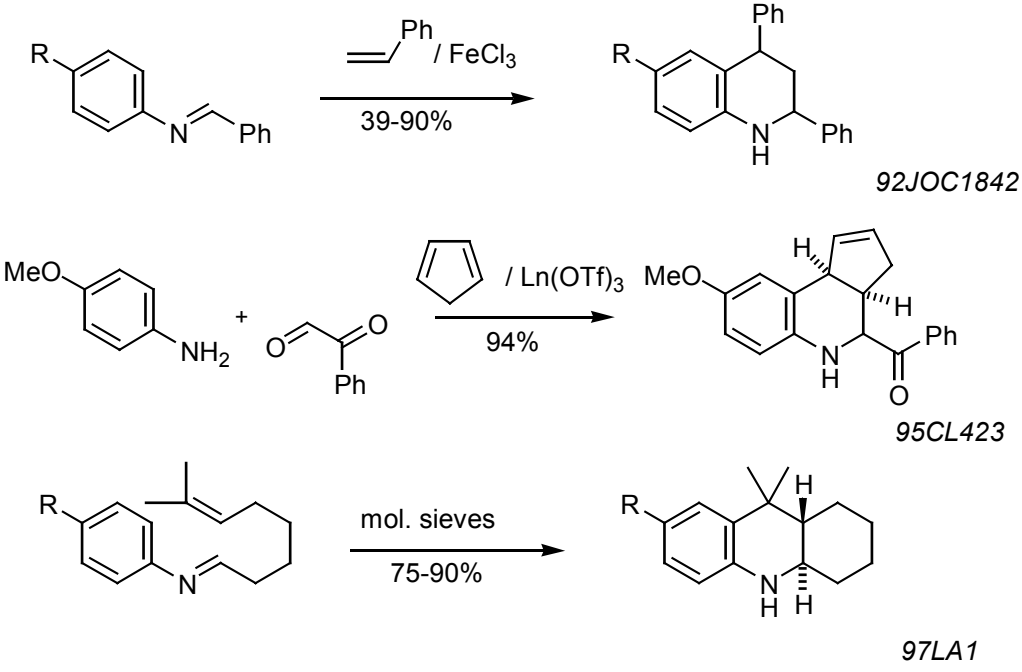
up to 92% in Heck reaction using Ph_3As ligand on Pd → *Namyslo, Kaufmann, 99SL114*

use of chiral ligands on Pd gives up to 81% *ee* → *Namyslo, Kaufmann, 99SL804*

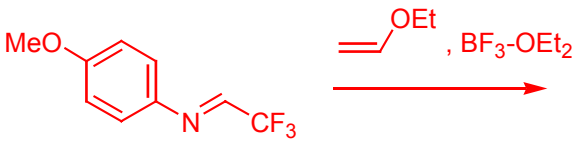
Examples of acyclic azadienes in cycloaddition reactions



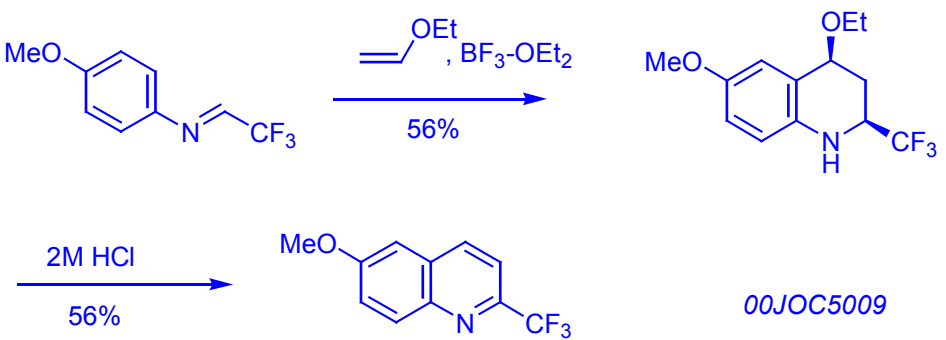
Aniline imines as "azadienes"



Problem: **Suggest a structure for the product of the following reaction.**

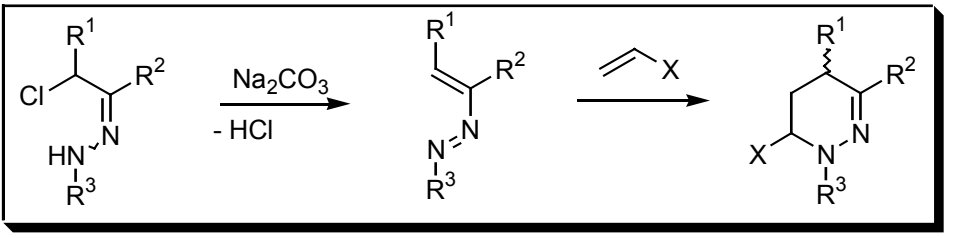


Answer: **This is a catalyzed cycloaddition (in this example, specifically *endo*). The cycloadduct is converted into 6-methoxy-2-trifluoromethylquinoline by further reaction with dil. HCl.**

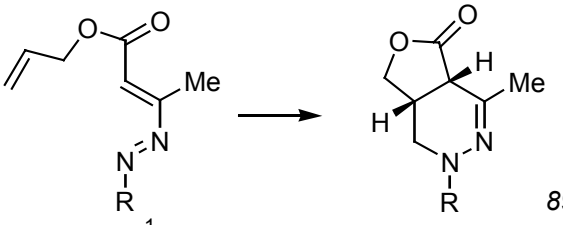


00JOC5009

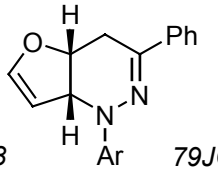
Vinylazo intermediates as dienes



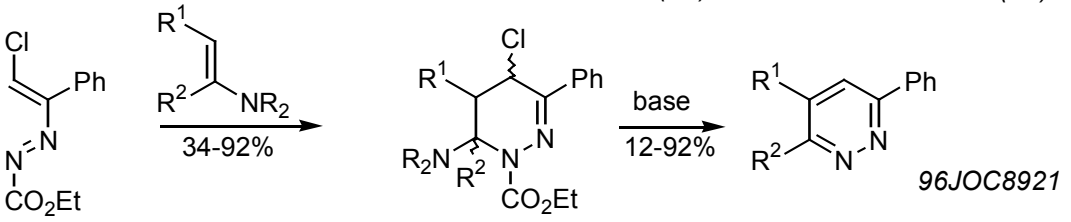
Review: Attanasi, Caglioti, 86OPP299



89JCS(P1)353

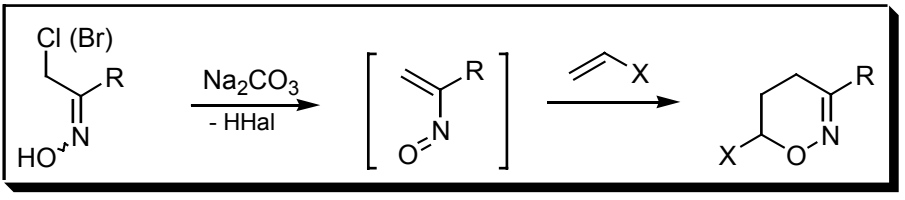


79JCS(P1)249



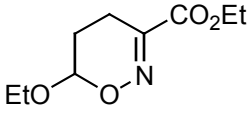
96JOC8921

Vinylnitroso intermediates as dienes

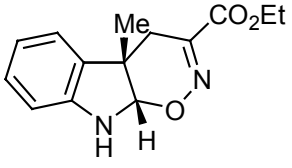


Review: Gilchrist, Wood, Comp. Het. Chem. II, 1996,6, 279

Examples

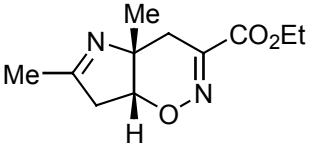


83JCS(P1)1283



(from 3-methylindole)

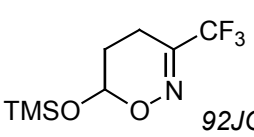
83JCS(P1)1283



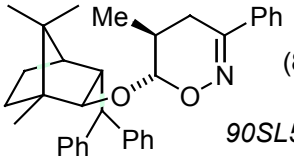
(from 2,5-dimethylpyrrole0)

93JCS(P1)1391

Note that the indole and pyrrole components act as dienophiles



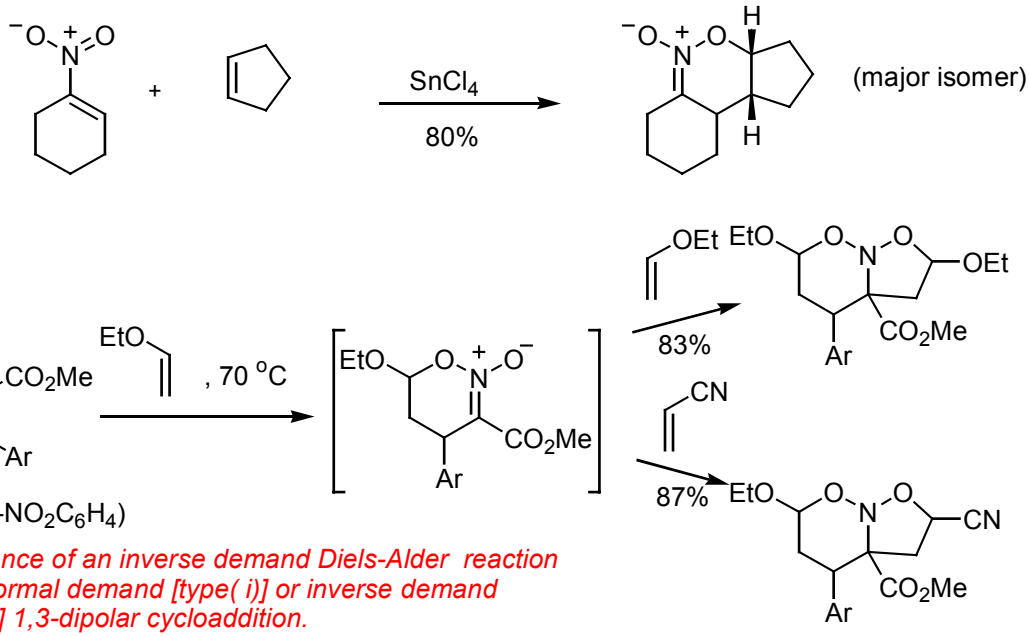
92JOC339



(88% *de*)

90SL514

Nitroalkenes as heterodienes



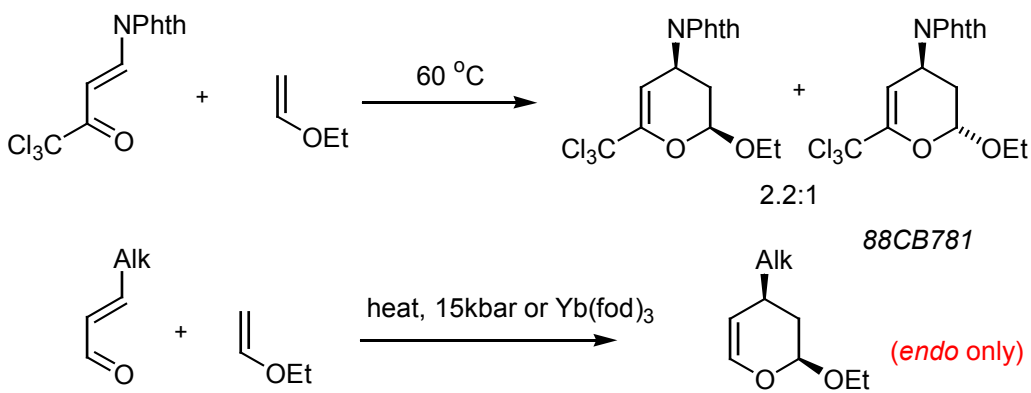
A sequence of an inverse demand Diels-Alder reaction and a normal demand [type(i)] or inverse demand [type (ii)] 1,3-dipolar cycloaddition.

Review: Denmark, Thorarensen, 96CRV137

Enones as dienes

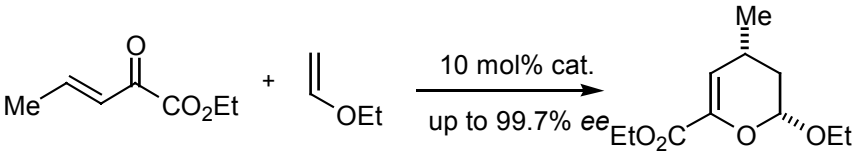
Diels-Alder reactions are of the "inverse demand" type so go best with enones bearing additional activating substituents and with electron rich dienophiles.

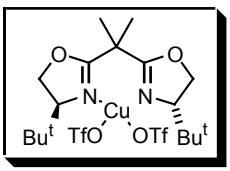
Simple enones usually require a Lewis acid catalyst or high pressure to react.



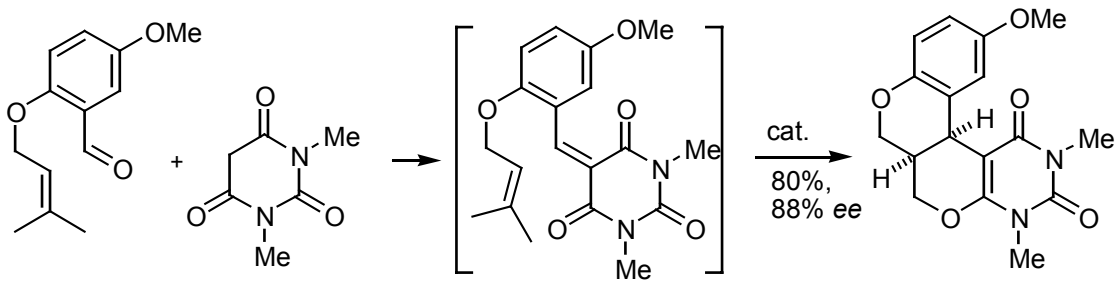
84TL721; 77JOC282

Catalytic enantioselective cycloaddition of enones





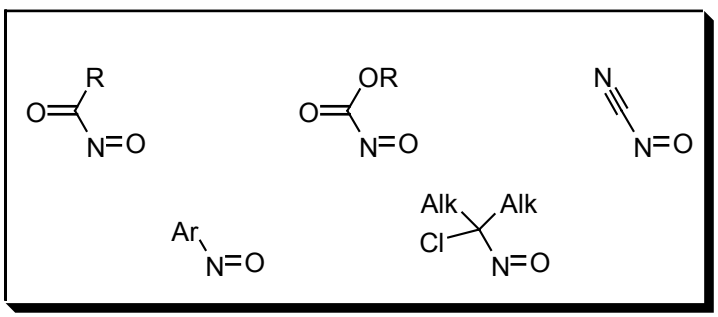
Jørgensen et al., 98AG(E)2404
Related: Evans, Johnson, 98JA4895



cat. diacetoneglucose + $Ti(OPr^i)_4$

Tietze, Saling, 92SL281
Review: Tietze, 96CRV115

Nitroso dienophiles



Arylnitroso compounds are rather poor dienophiles unless an electron withdrawing substituent is present.

Acylnitroso compounds, nitroso esters and nitrosyl cyanide are among the most reactive dienophiles known.

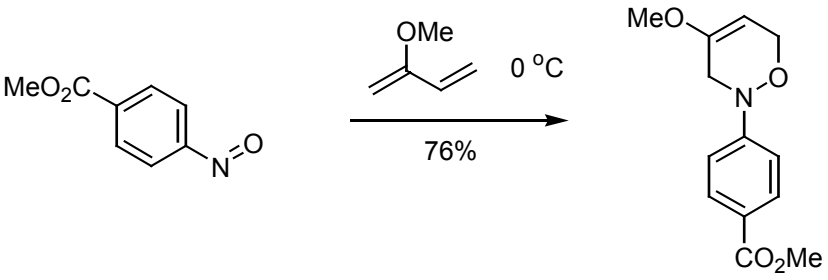
α-Chloroalkylnitroso compounds are useful because the substituent is easily removed from the adduct.

Chiral dervatives are readily available and selectivity can be high.

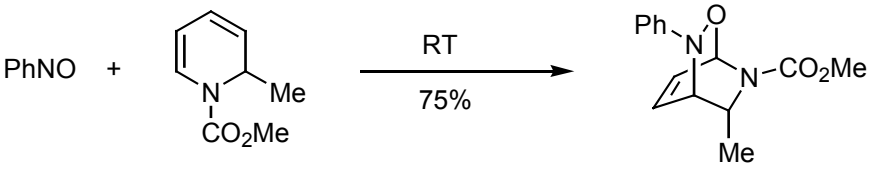
Adducts are useful because the N-O bond is easily cleaved.

Review: Streith, Defoin, 94S1107

Arylnitroso compounds as dienophiles

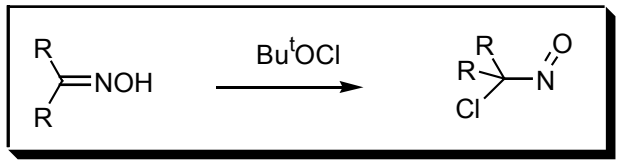


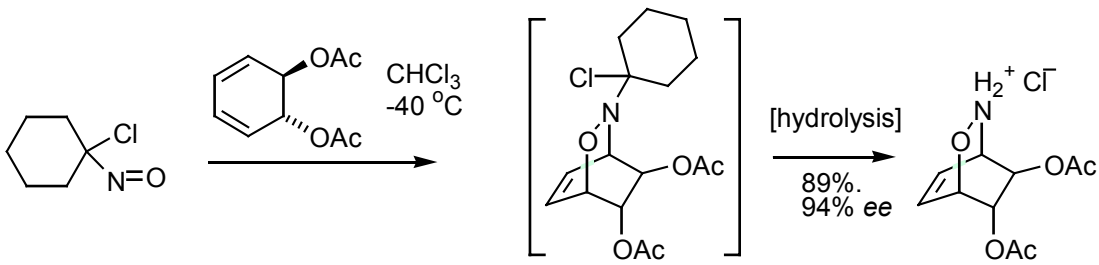
Taylor et al., 82JOC552



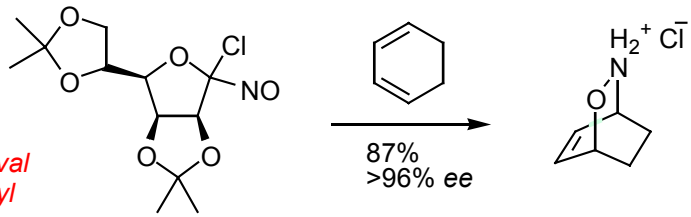
Streith et al., 85HCA95

α-Chloroalkylnitroso compounds





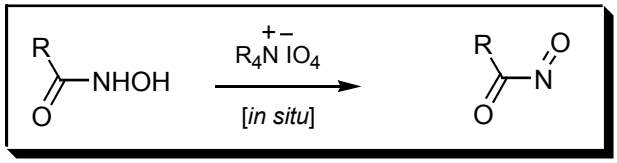
90LA267



91HCA103

Note the easy hydrolytic removal of the chloroalkyl groups

Acylnitroso compounds

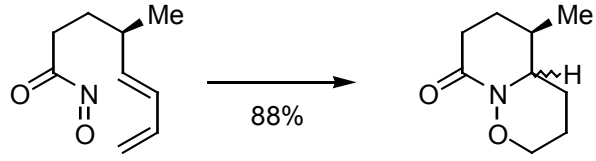


Although these are only transient intermediates they are superb electron deficient dienophiles

A disadvantage of the Diels-Alder reaction: regioselectivity is not great; e.g.

85JOC1911

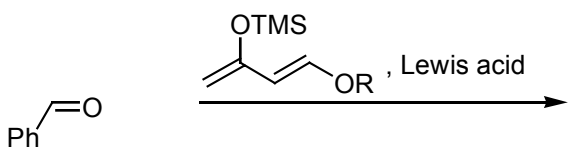
Not a problem if intramolecular; e.g.



64% H cis to Me, 36% trans

92JOC2876

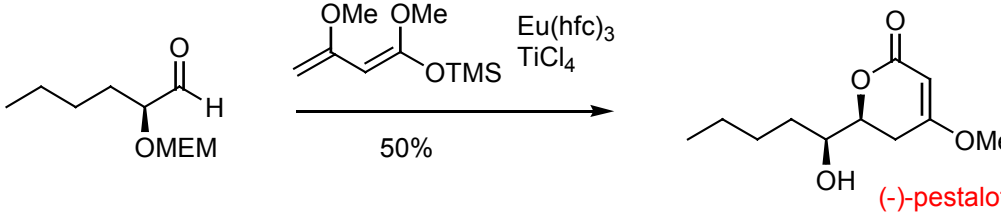
Simple (unactivated) aldehydes as dienophiles



(major isomer with lanthanides as Lewis acids)

Chiral shift reagents lead to products with moderate enantioselectivity

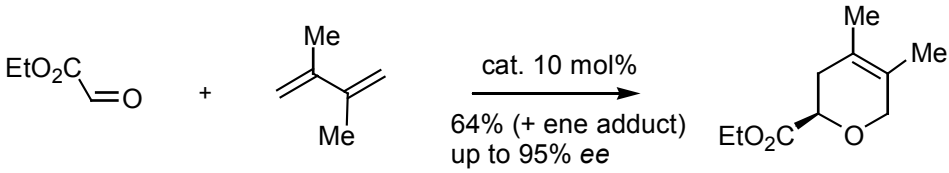
Danishefsky et al., 83TL3451, 86JA7060, 87AG(E)15



(-)-pestalotin

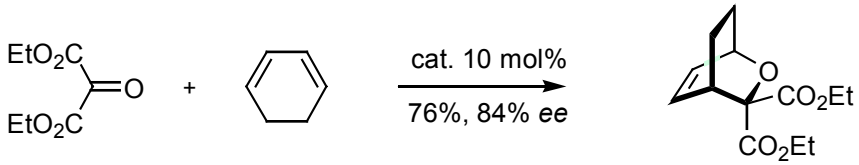
Midland, Graham, 84JA4294

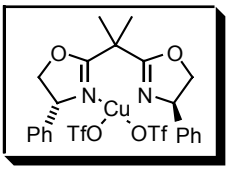
Catalytic enantioselective cycloaddition: oxo dienophiles



Me_2AlCl - polyBINOLate cat.

Johannsen, Jørgensen et al.,99JOC299



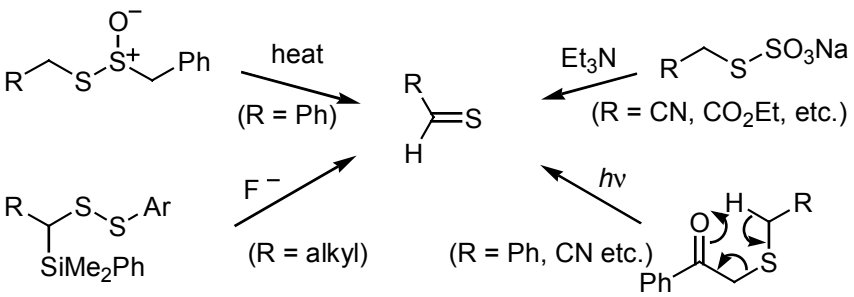


Jørgensen et al., 99JOC6677

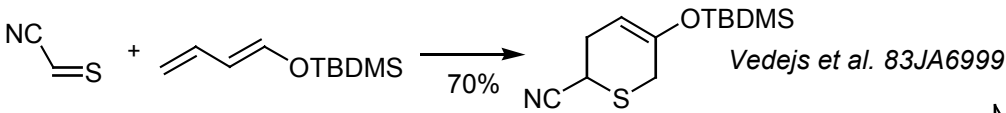
Review: Jørgensen, 00AG(E)3959

Thiocarbonyl compounds: excellent dienophiles

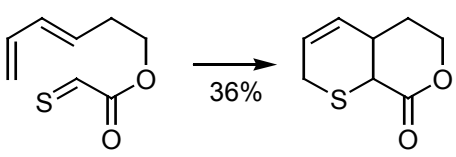
Thioaldehydes:



Reviews: 92AHC(55)1, 93CSR199

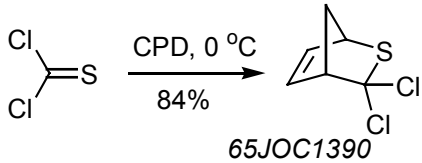


Vedejs et al. 83JA6999



cis:*trans* 19:1

88JOC2220

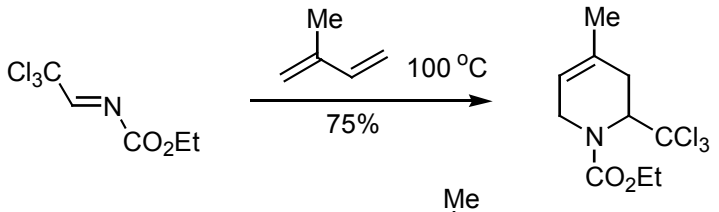


65JOC1390

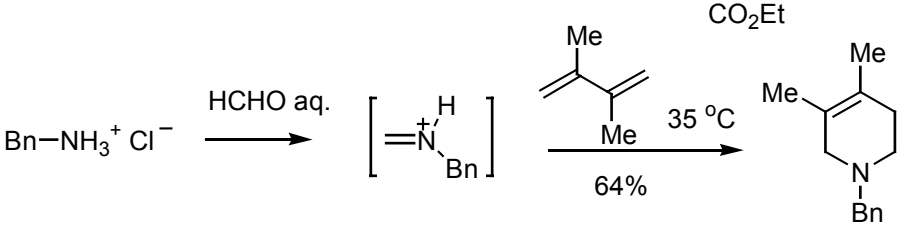
See also 96EJOC2861,2875

Examples of imines and nitriles as dienophiles

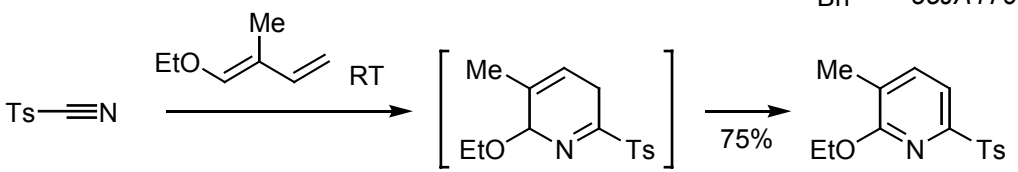
"Normal electron demand" cycloaddition



73BCJ2922

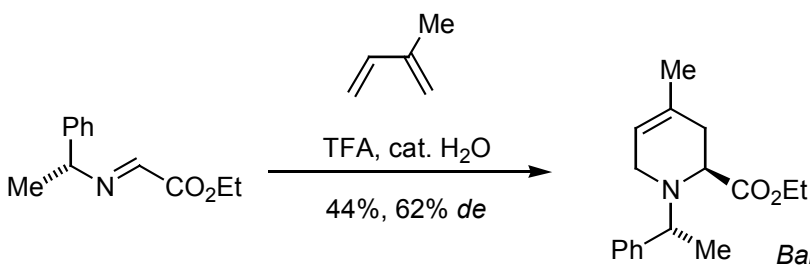


85JA1768

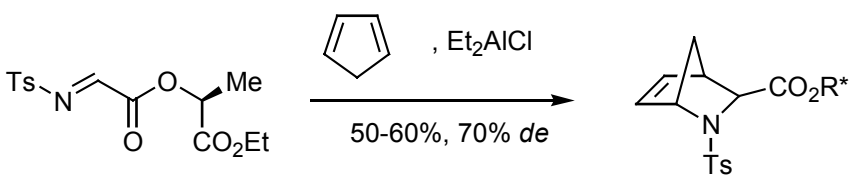


89S623

Aza dienophiles with chiral auxiliariies



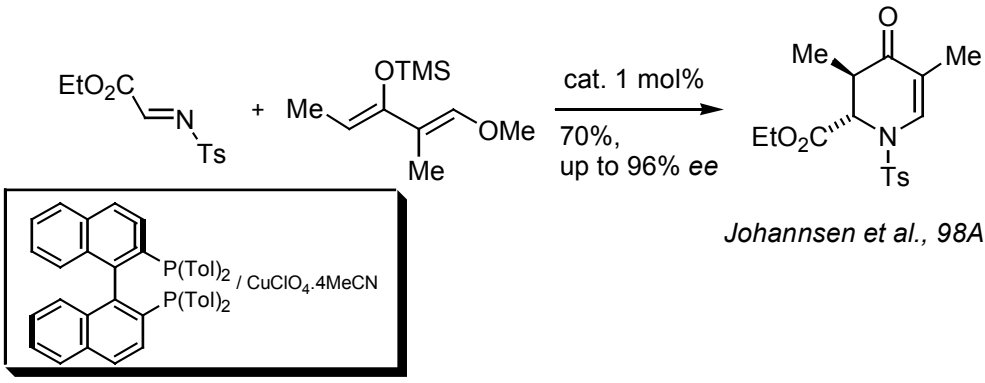
Bailey et al., 91TAS1263



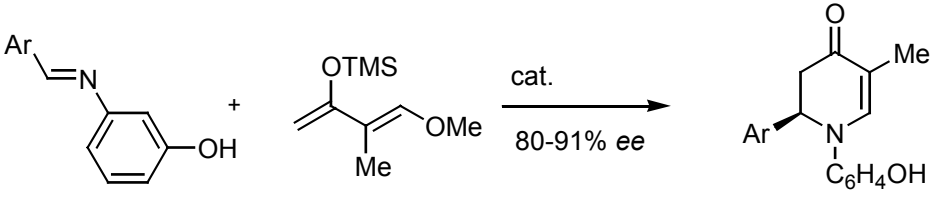
Holmes et al., 92CC786

Reviews: Bailey et al., 98CC633, Waldmann, 94S535

Catalytic enantioselective cycloaddition: imino dienophiles



Johannsen et al., 98AG(E)3121

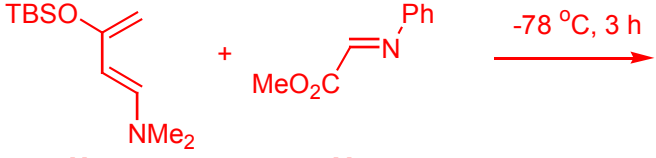


cat. BINOL + $Zr(OBu^t)_4$

Kobayashi et al., 99JOC4220

Review: Jørgensen, 00AG(E)3959

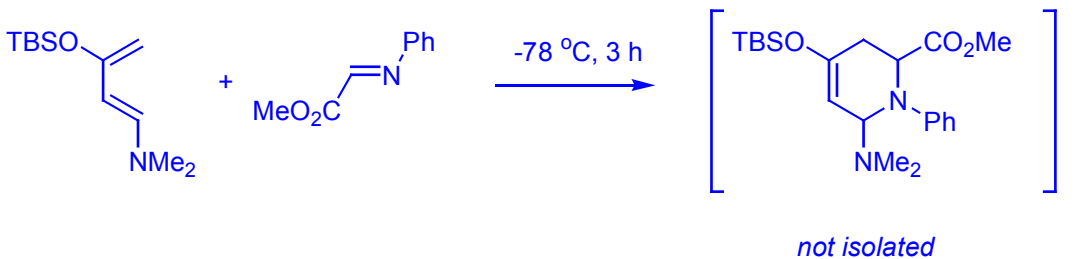
Problem: **The diene X undergoes an uncatalyzed addition to the imine Y at –78 °C. Predict the reaction product (after aqueous acidic hydrolysis) and account for the high reactivity of the diene.**



X **Y**

(TBS = *tert*-butyldimethylsilyl)

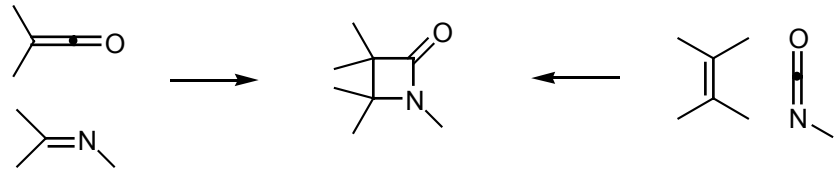
Answer: **The reaction sequence is shown. The diene is remarkably nucleophilic because of the combined electron donating effects of the dimethylamino and silyloxy substituents.**



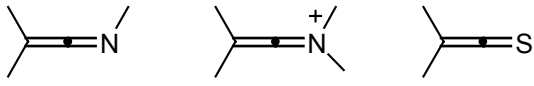
Huang, Rawal, 00 OL3321

[2 + 2] Cycloaddition

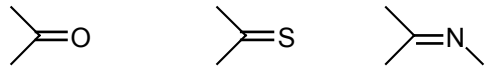
Most of the useful thermal reactions involve cumulenes (ketenes, isocyanates, *etc.*) as reagents.



and



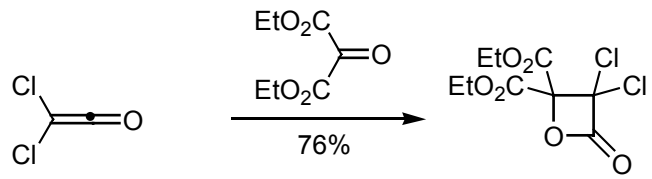
with

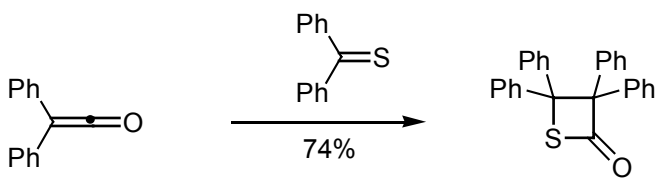


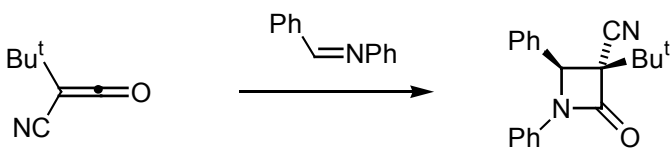
Other useful reactions are limited to specific ring systems, *e.g.*
1,2-dioxetanes from singlet oxygen addition to alkenes
oxetanes from photochemical addition of carbonyl compounds to alkenes (Paterno-Büchi reaction)

Review: Ghosez et al., Comp. Org. Synth. 1991, 5, 85

Heterocycles by ketene cycloaddition

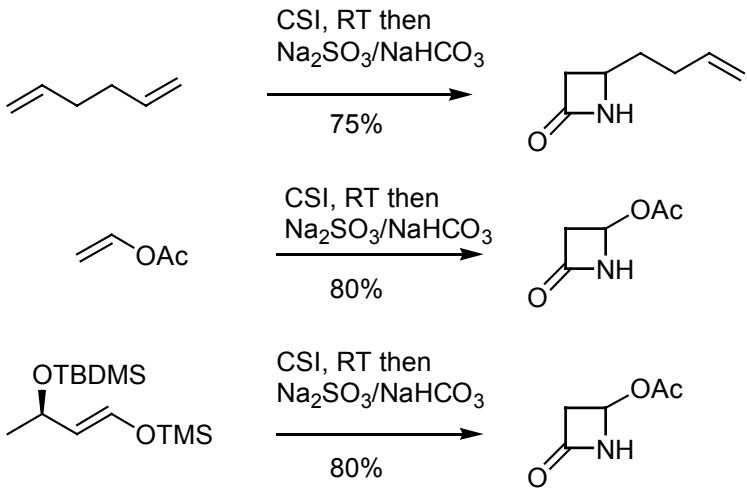






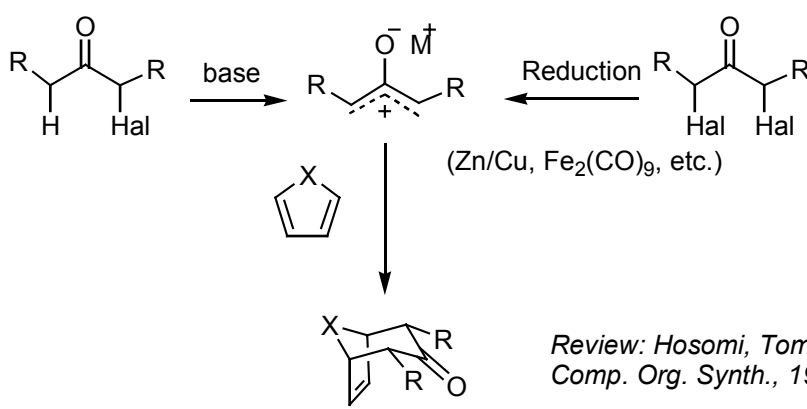
(see the Ghosez review for discussion of stereoselectivity)

Cycloaddition of chlorosulfonyl isocyanate (CSI)

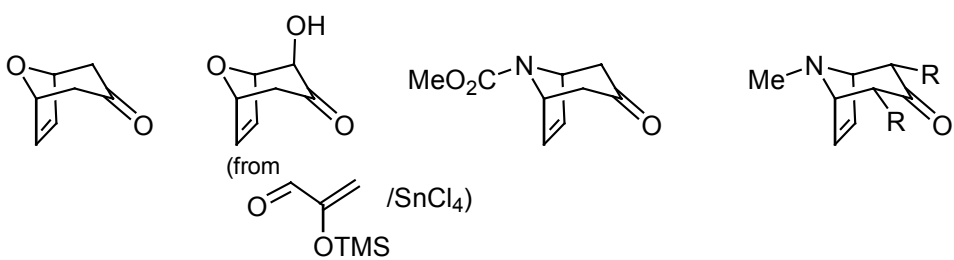


Reviews: Dhar, Murphy, 86S437; Chmielewski et al., 86CC2689

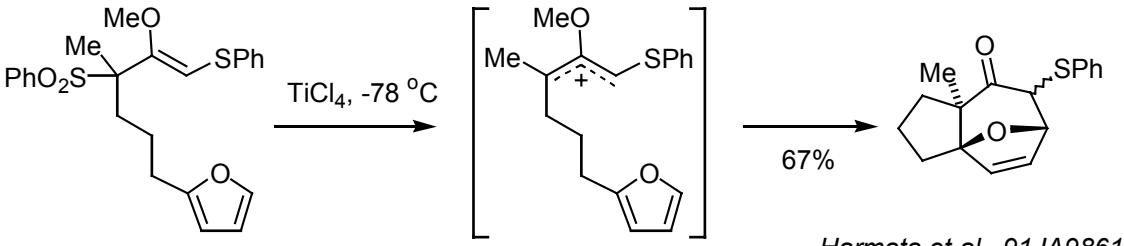
[4 + 3] Cycloaddition



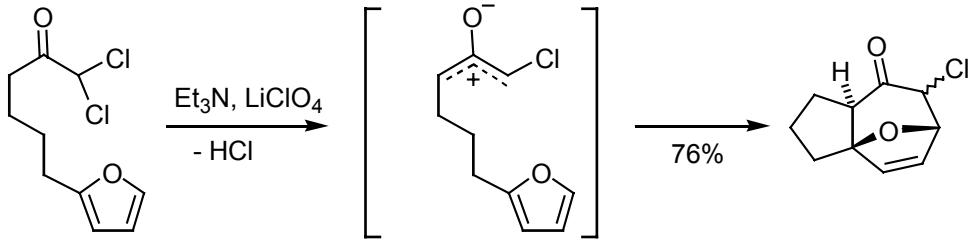
Review: Hosomi, Tominaga, Comp. Org. Synth., 1991, 5, 593



Intramolecular [4 + 3] cycloaddition



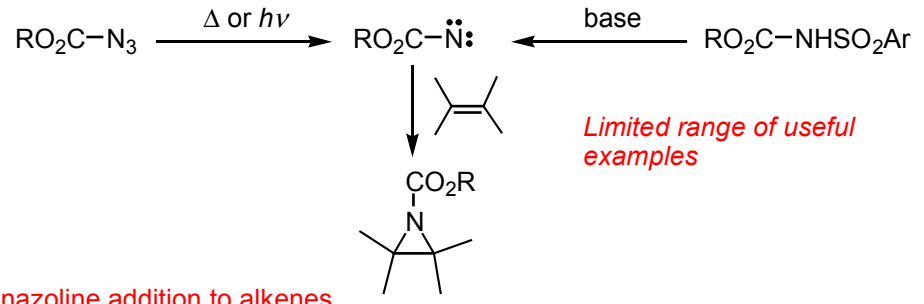
Harmata et al., 91JA9861
Review: Harmata, 97T6235



Föhlisch, Herter,
84CB2580

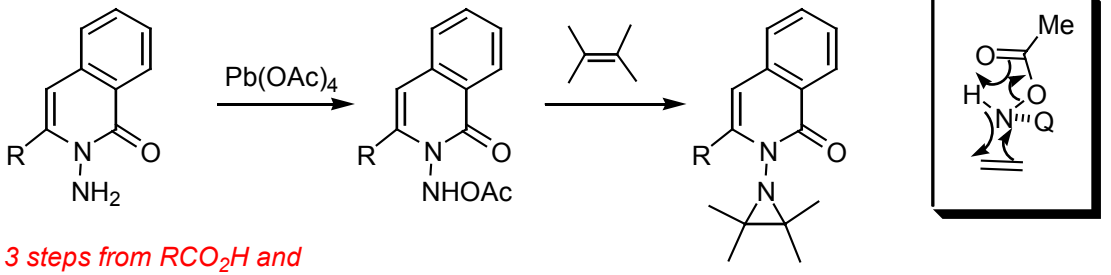
[2 + 1] cycloaddition: aziridination of alkenes

Nitrene addition to alkenes



Limited range of useful examples

N-Acetoxyaminoquinazoline addition to alkenes



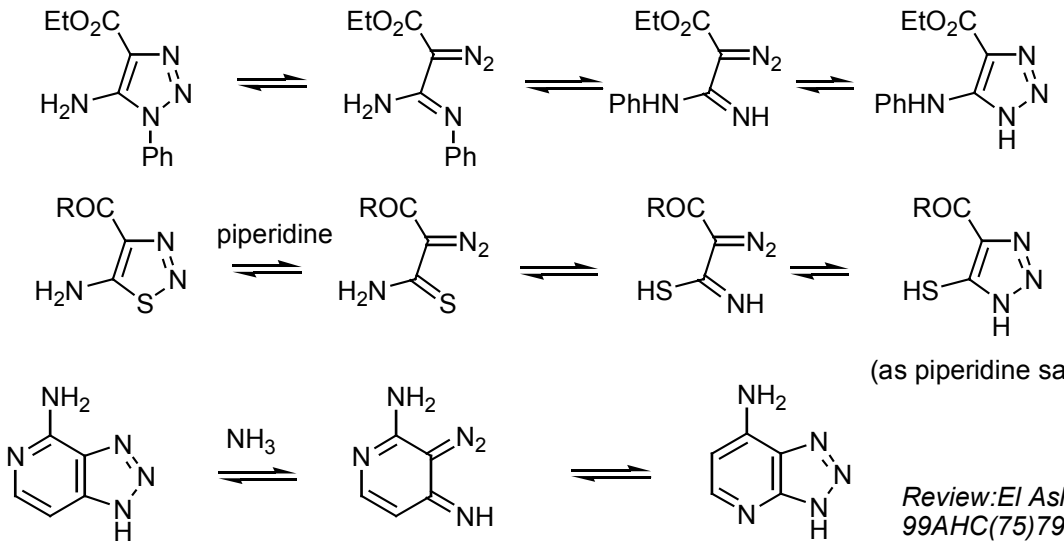
3 steps from RCO_2H and anthranilic acid
Chiral R leads to chiral adducts (selective)

Review: Atkinson, 99T1519

3 Ring interconversion and some ring modification methods

Many useful heterocyclic syntheses involve the conversion of one ring system into another: some representative examples are given in this section. Some useful ring modifications, particularly oxidations and reductions, are also illustrated.

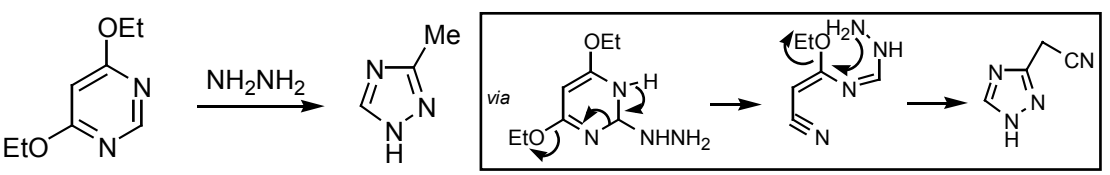
Dimroth rearrangement



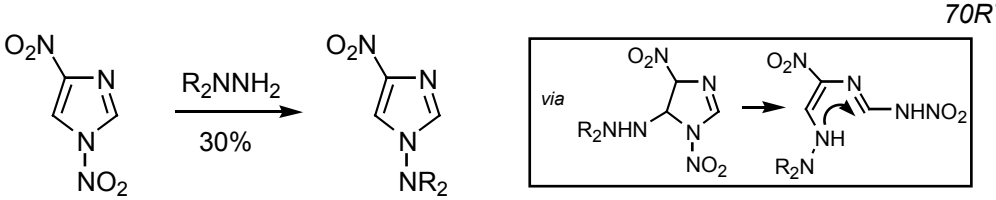
Review:El Ashry et al., 99AHC(75)79

Ring interconversion via the S_N(ANRORC) mechanism

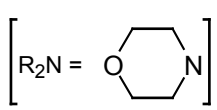
(ANRORC = Addition of Nucleopile, Ring Opening, and Ring Closure)



70RTC680

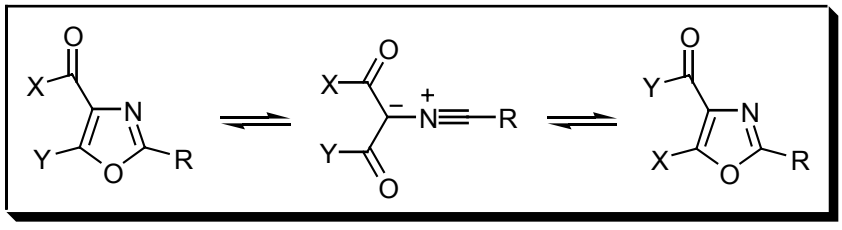


96T14905

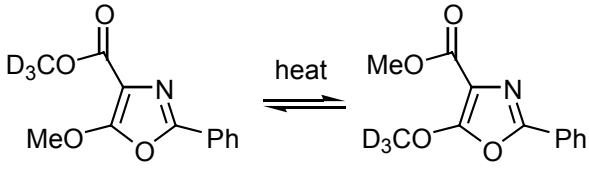


Review: van der Plas, 99AHC(74)1

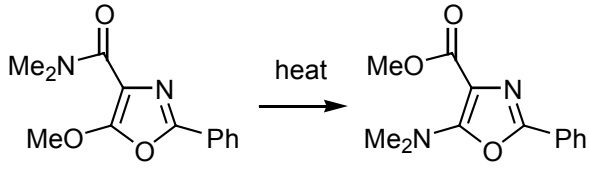
The Cornforth rearrangement of oxazoles



Mechnistic evidence from labelling:

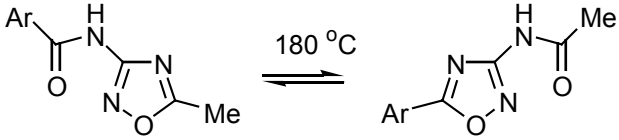


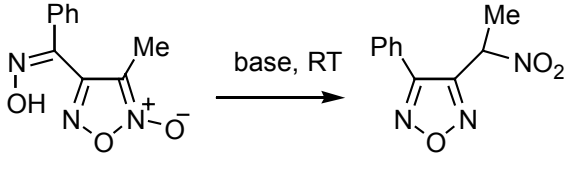
Example of the forward reaction:

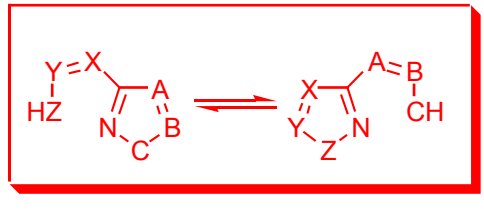


Review:
Taylor, Turchi, 79CRV181

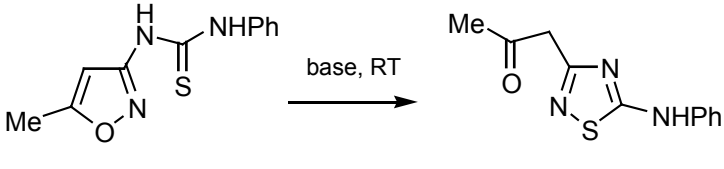
The Boulton-Katritky rearrangement and related reactions





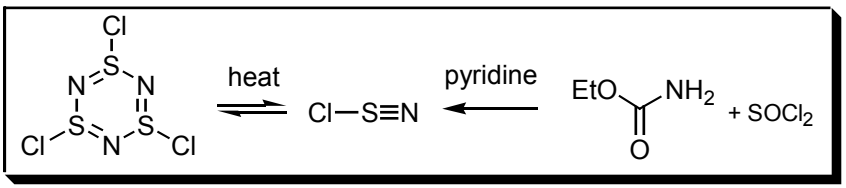


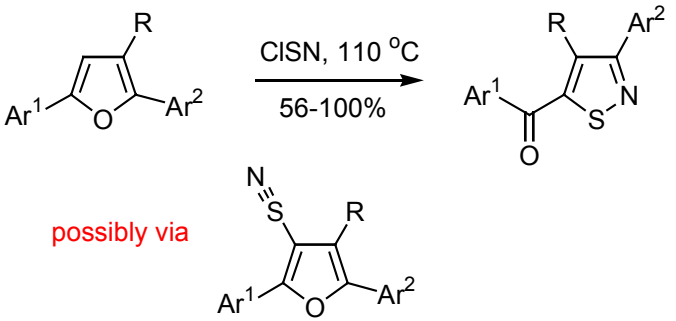
Z-oxime only (E oxime does not rearrange)



Reviews: Vivona et al., 93AHC(56)49; van der Plas, 99AHC(74)1

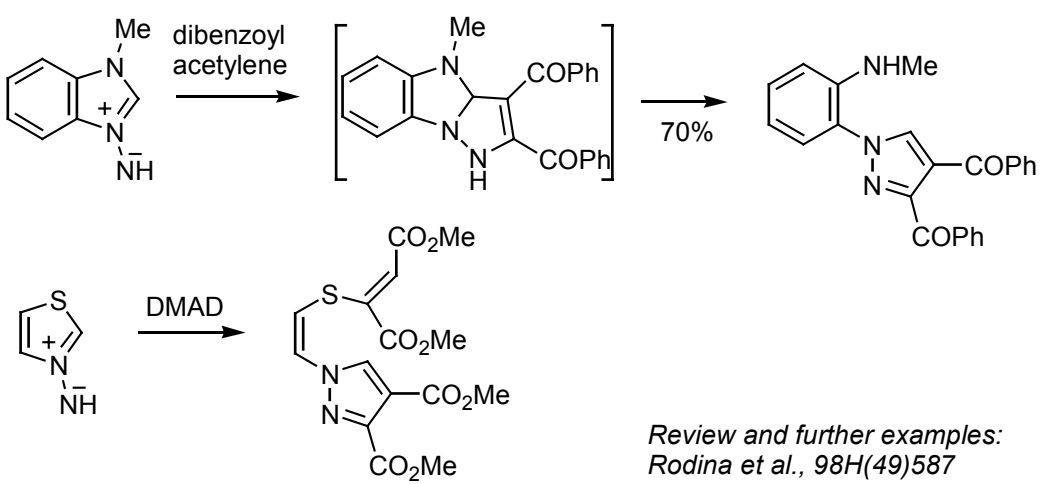
Isothiazoles from 2,5-diarylfurans and thiazyl chloride





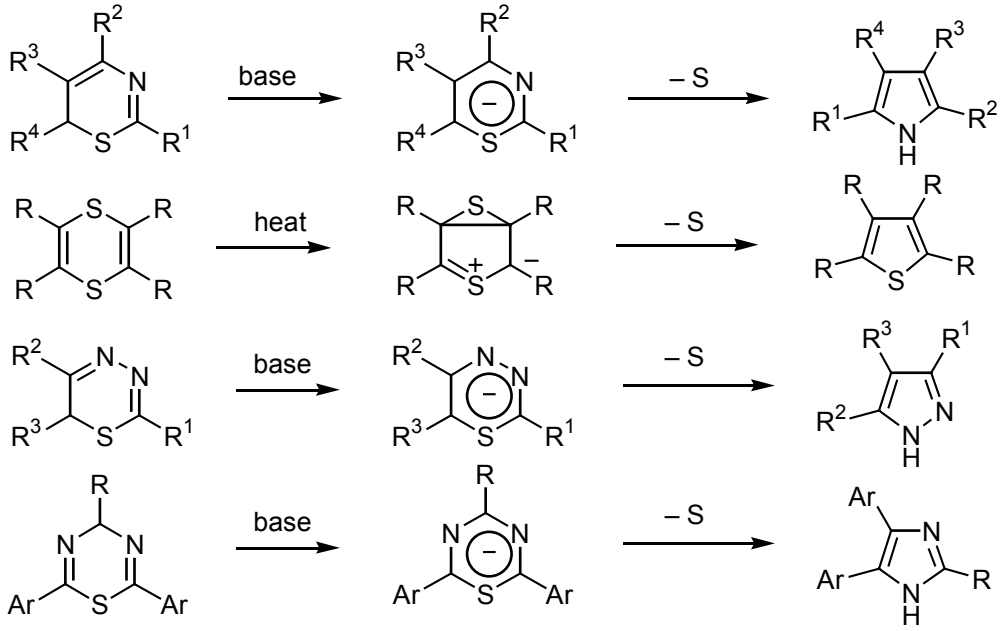
Laaman, Meth-Cohn, Rees, 99S757

Rearrangement following dipolar addition of azolium ylides



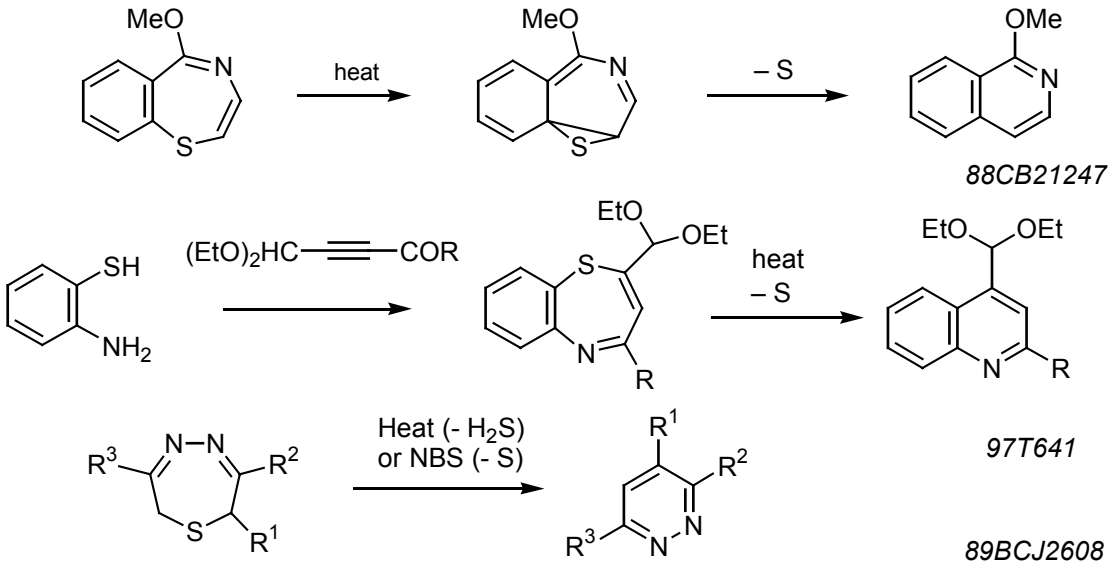
Review and further examples:
Rodina et al., 98H(49)587

Ring contraction to 5-membered rings by sulfur extrusion



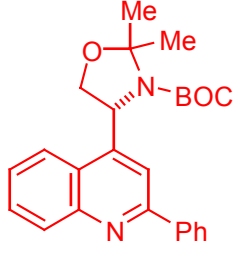
Review and further examples: Bohle, Liebscher, 96AHC(65)39

Ring contraction to 6-membered rings by sulfur extrusion



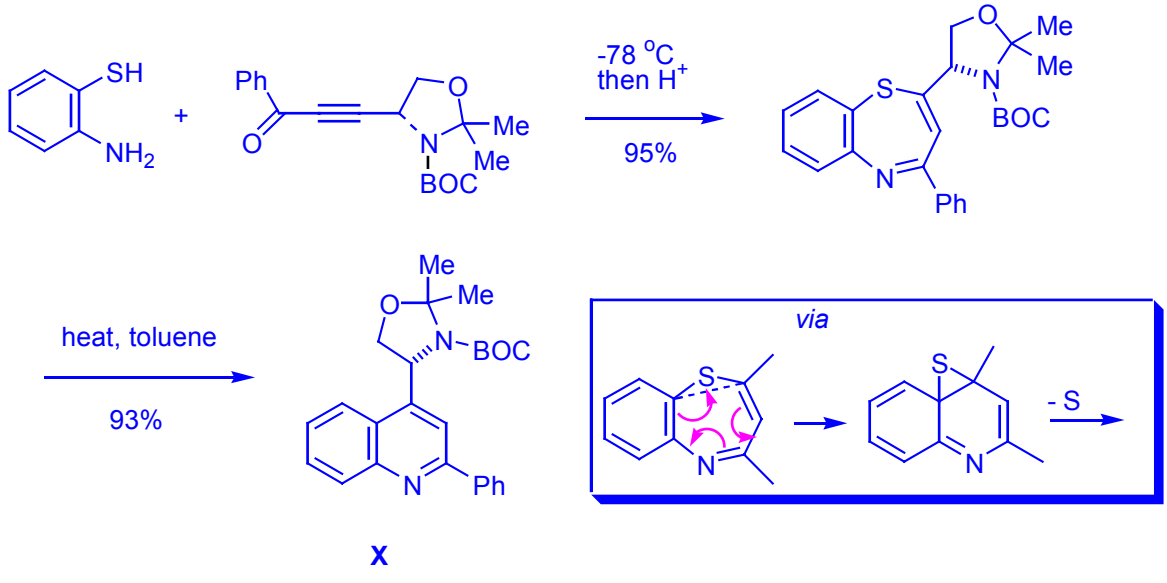
Review and further examples: Bohle, Liebscher, 96AHC(65)39

Problem: **Devise a synthesis of the quinoline X from 2-aminothiophenol.**



X

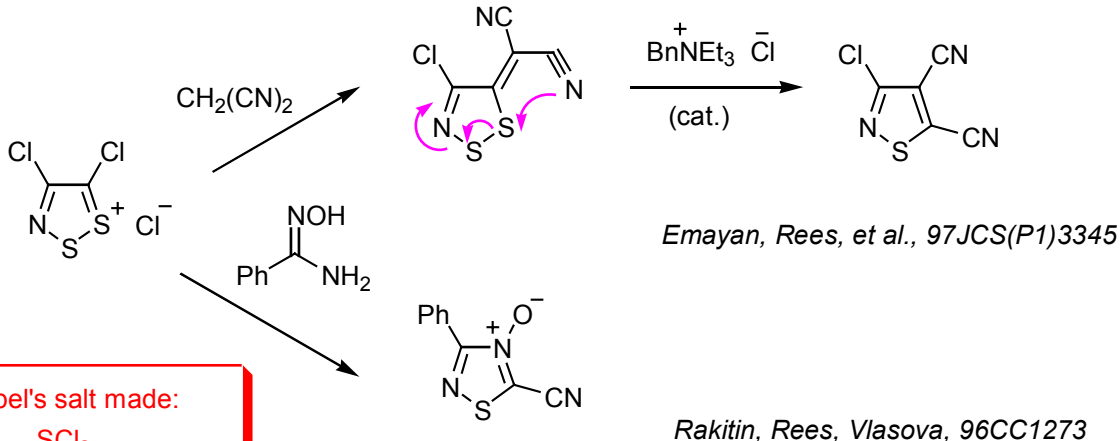
Answer:



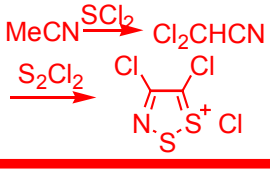
X

00SL595

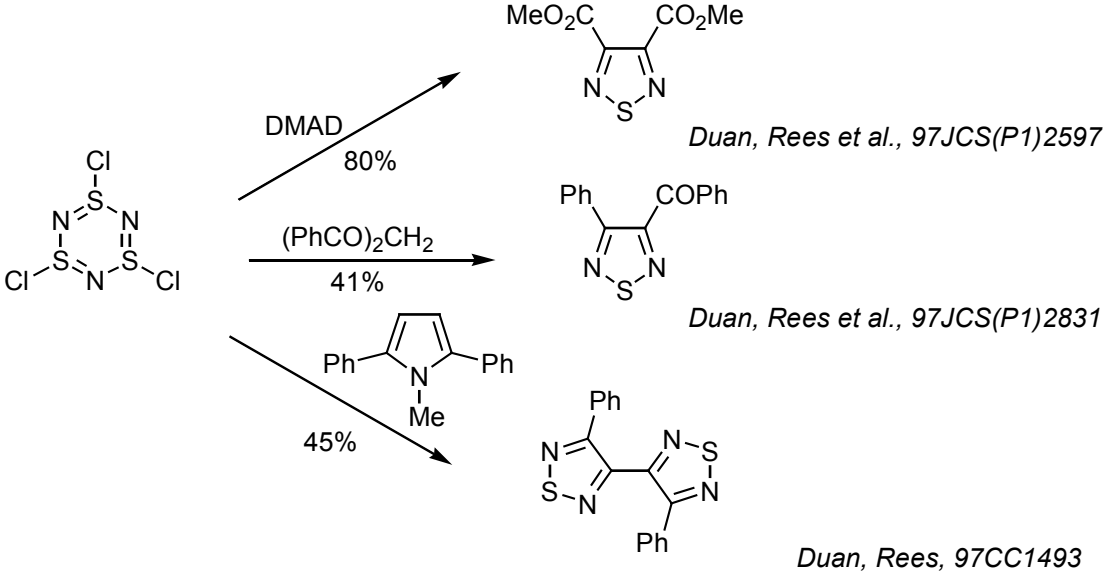
Appel's salt for the synthesis of nitrogen-sulfur heterocycles



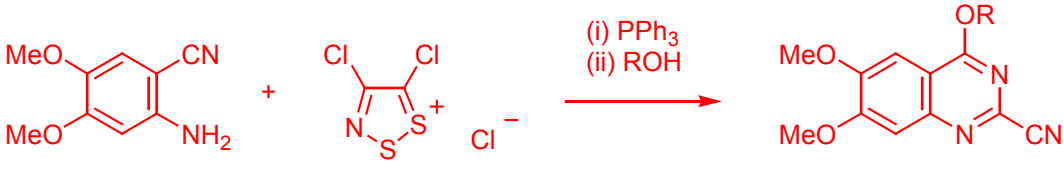
Appel's salt made:



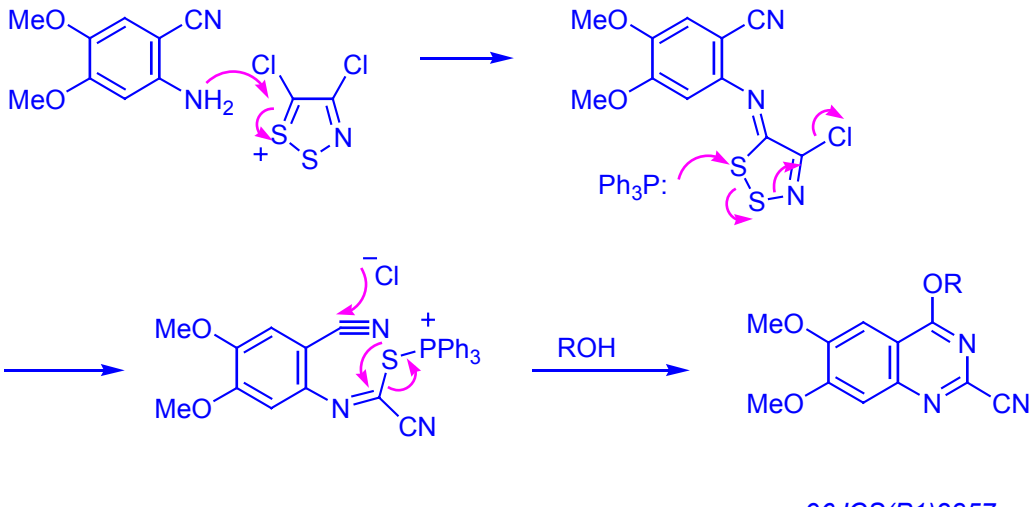
1,2,5-Thiadiazoles from trithiazyl chloride



Problem: **Explain**

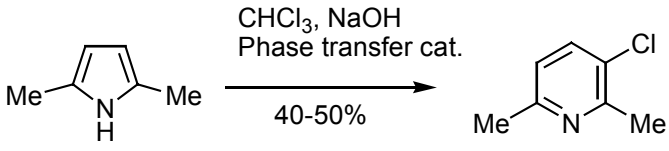


Answer: **a possible mechanism:**

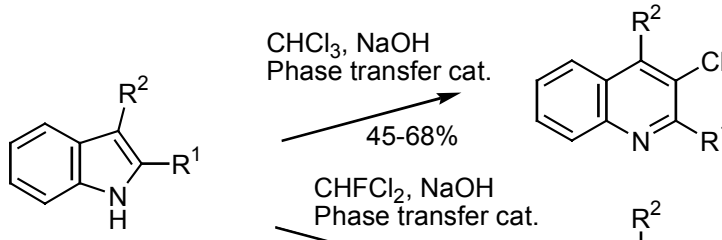


96JCS(P1)2857

Ring expansion via carbenes: pyrroles and indoles



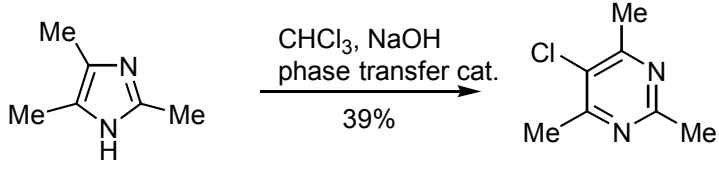
76S798



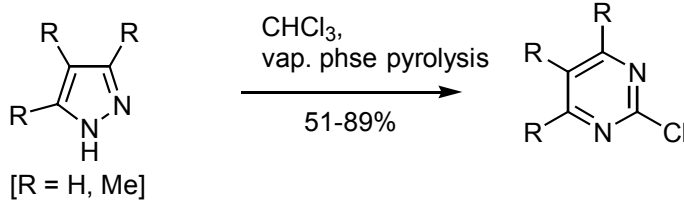
76S249, 76S798

76LA1456

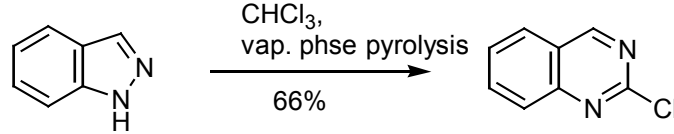
Other ring expansions induced by dichlorocarbene addition



76S798

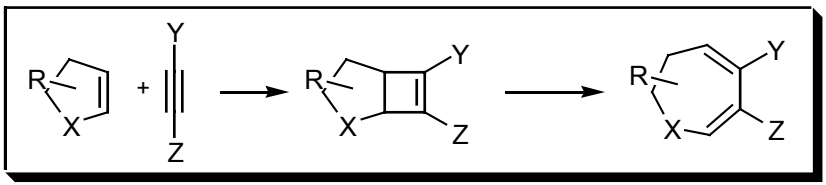


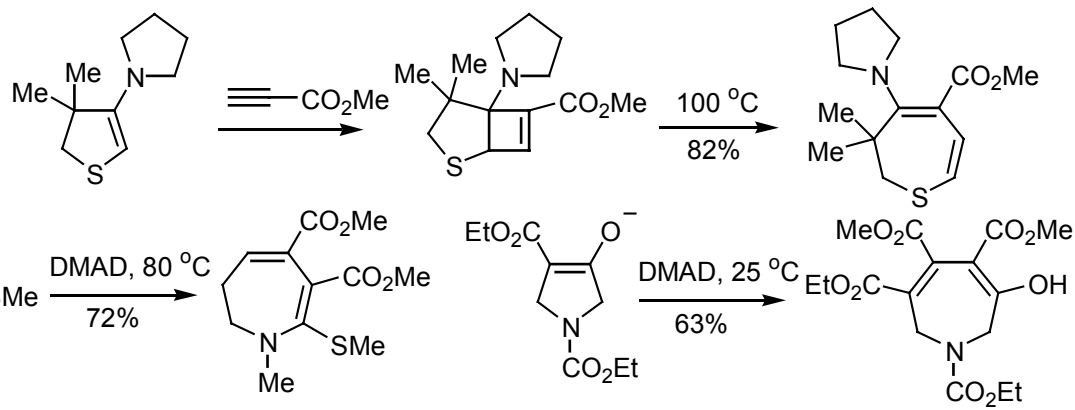
79JCS(P1)2786



79JCS(P1)2786

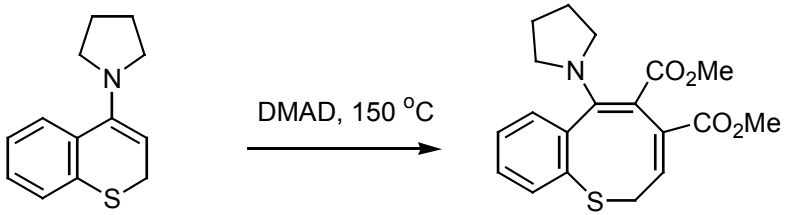
[2 + 2] Addition and ring opening: 7 membered heterocycles



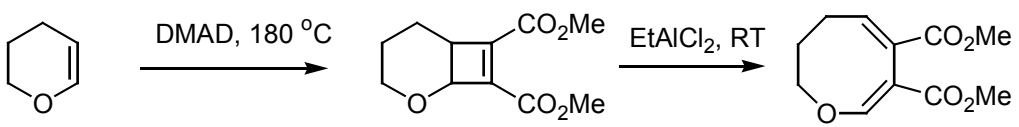


Review: Hassenrück, Martin, 88S569

[2 + 2] Addition and ring opening: 8 membered heterocycles

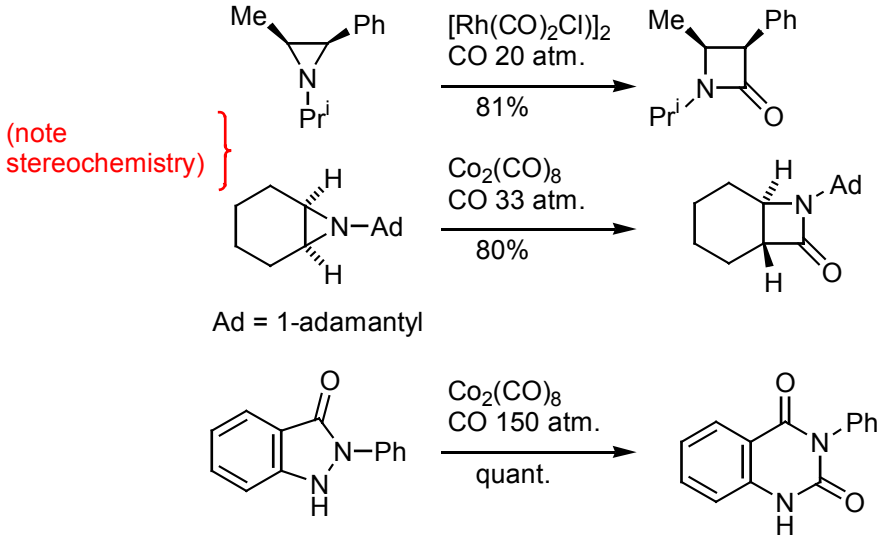


Lamm et al., 82ACS(B)435



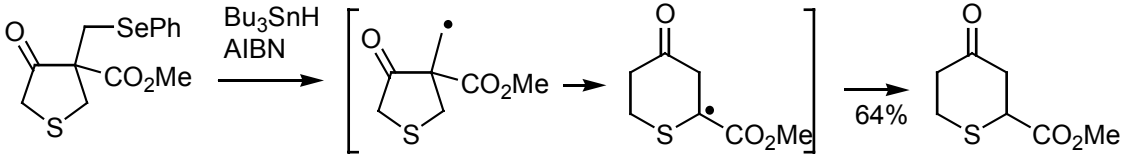
Nicolaou et al., 87TL1501

Carbonylative ring expansion of heterocycles

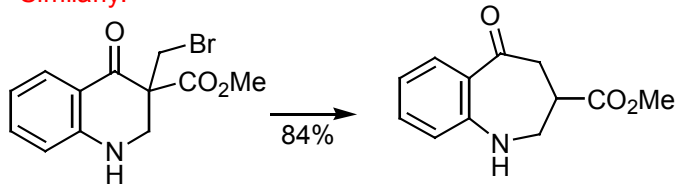


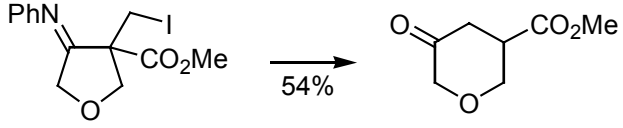
Review: Khumtaveeeporn, Alper, 95ACR414

Radical induced ring expansion of heterocycles



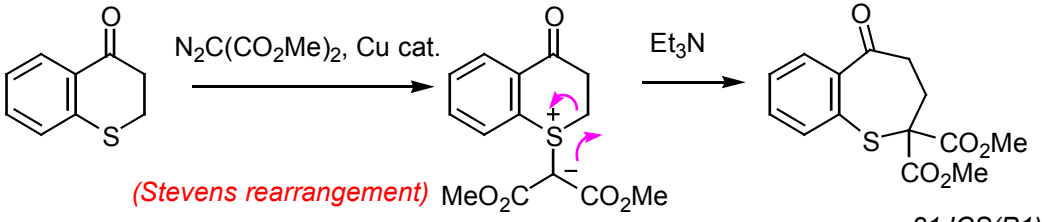
Similarly:



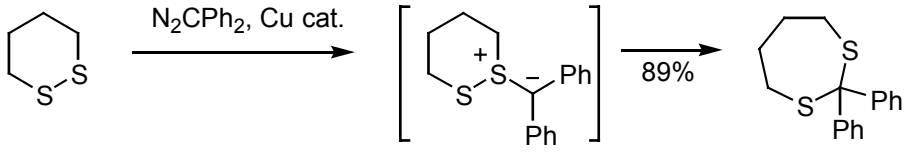


Review and further examples: Dowd, Zhang, 93CRV2091

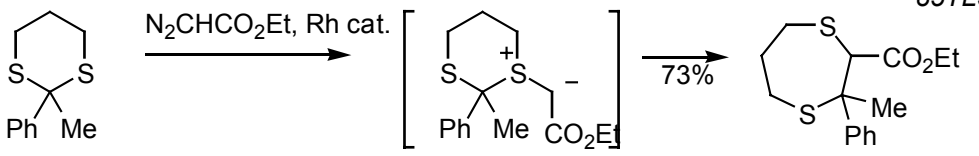
Ring expansion of sulfonium ylides to give 7-membered sulfur heterocycles



81JCS(P1)2978

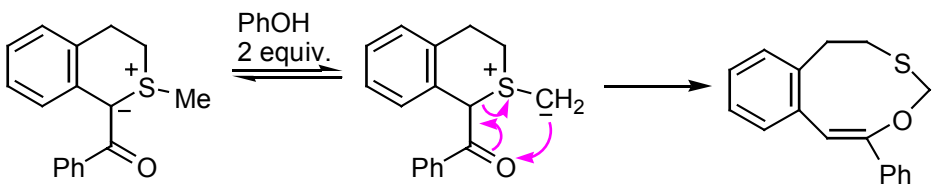


85TL5187

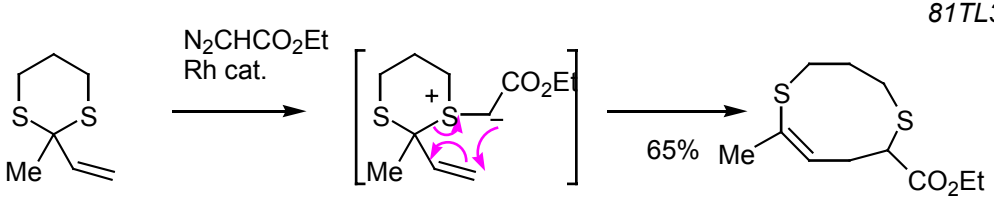


84JOC1917

Ring expansion of sulfonium ylides to give medium ring sulfur heterocycles



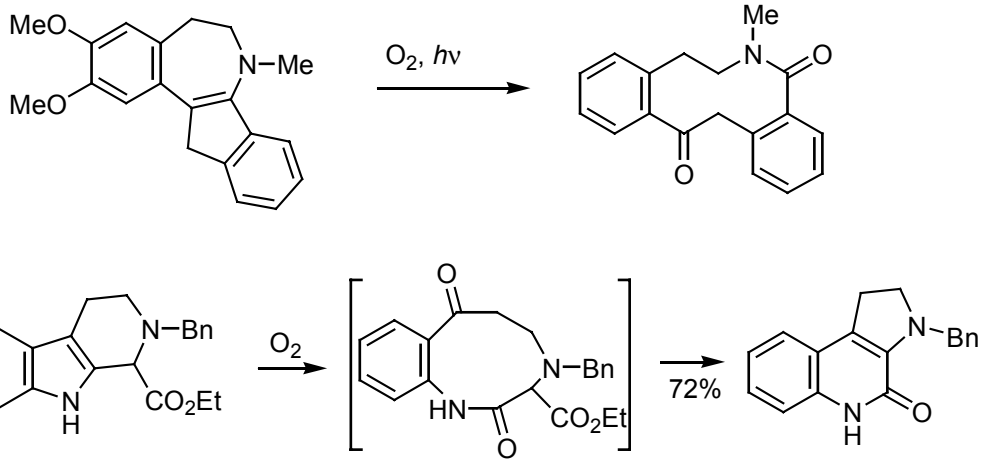
81TL3629



(Sommelet-Hauser rearrangement)

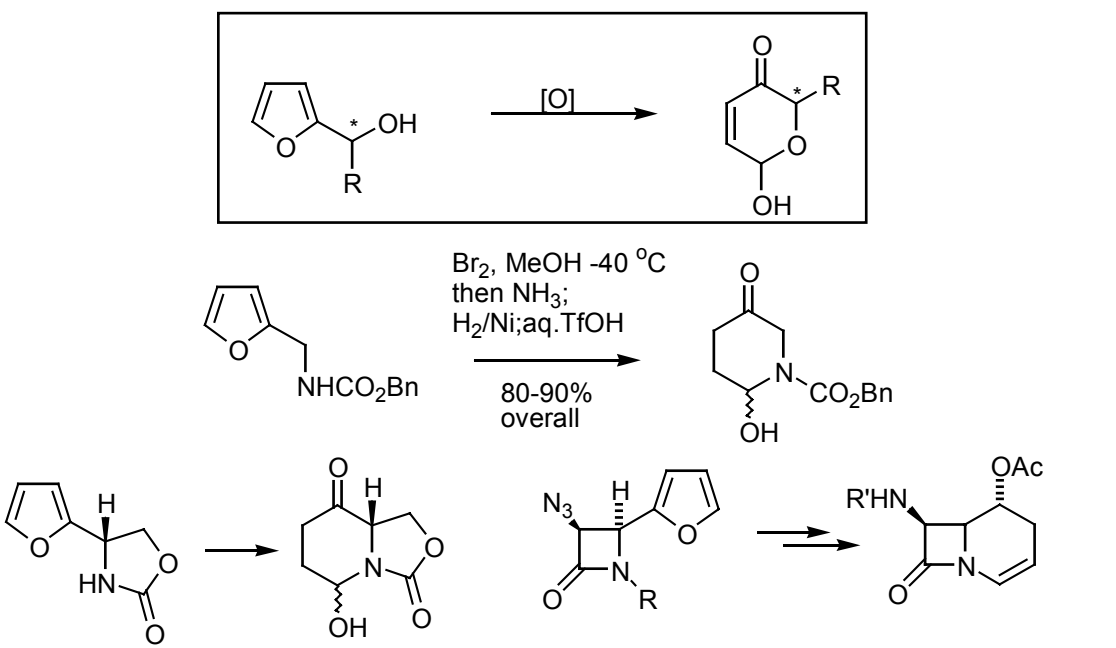
84JOC1917

Oxidative ring expansion



99SL563

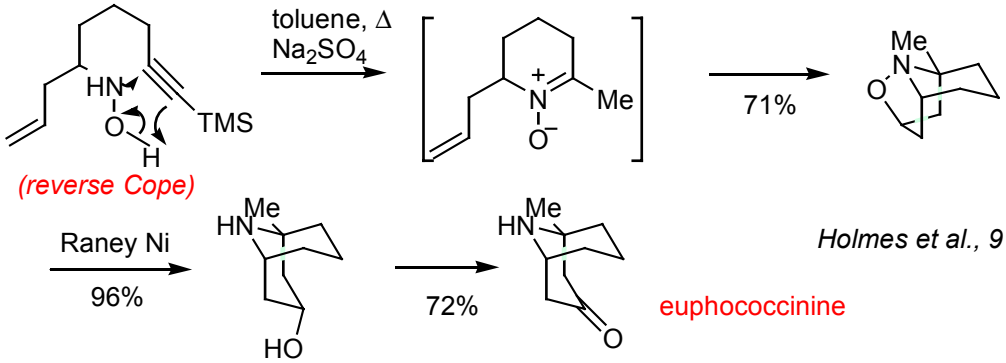
Oxidative ring expansion of amidoalkylfurans



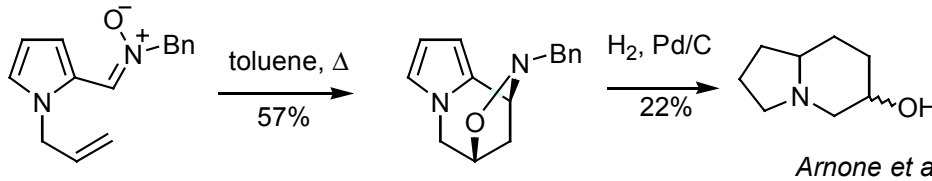
Review: Ciufolini et al., 98SL105

Reductive cleavage of isoxazolidine N-O bonds: examples of synthetic applications

Some methods of reductive cleavage: H_2/Pd, Na/Hg, Al/Hg, Raney Ni, $Mo(CO)_6$, Zn/AcOH

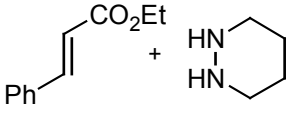


Holmes et al., 97PAC531

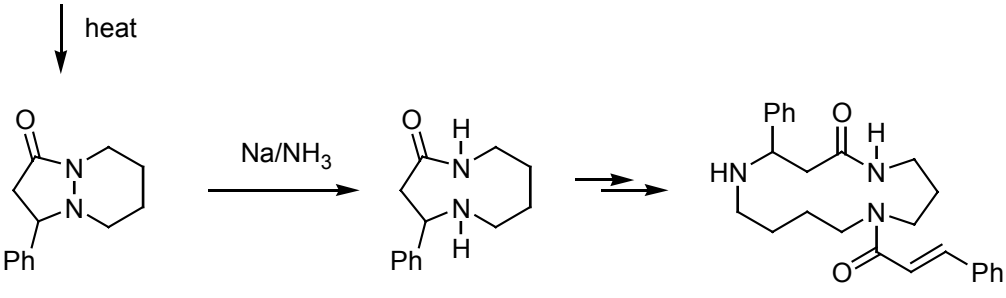


Arnone et al., 98JOC9279

Reductive cleavage of N-N bonds as a route to cyclic diamines



N-N bonds are difficult to cleave unless one or both nitrogens is activated by a carbonyl, sulfonyl or similar group.

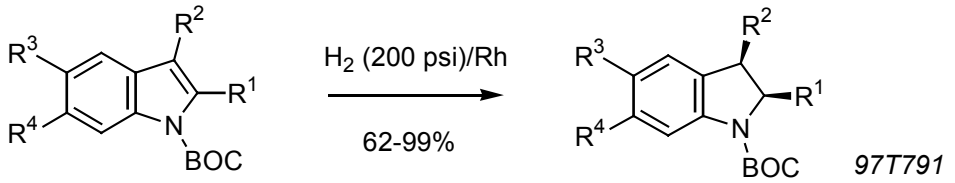


celacinnine

Wasserman et al., 80TL3493

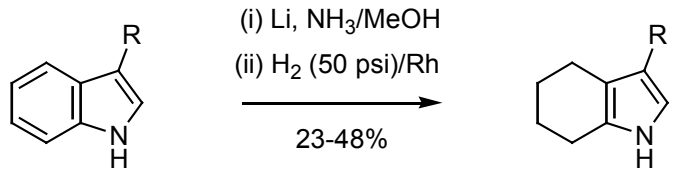
Related: 81JA461, 79JOC4473

Selective reduction: indoles and pyrroles

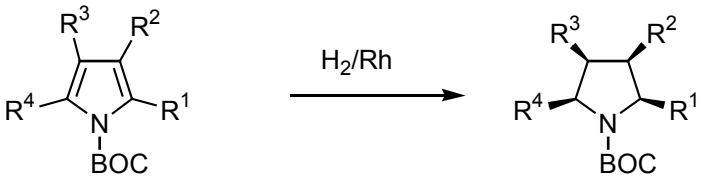


97T791

Indoles can also be reduced asymmetrically: 00JA7614

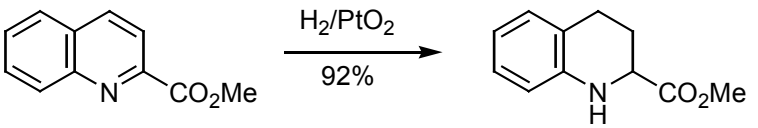


99TL8039



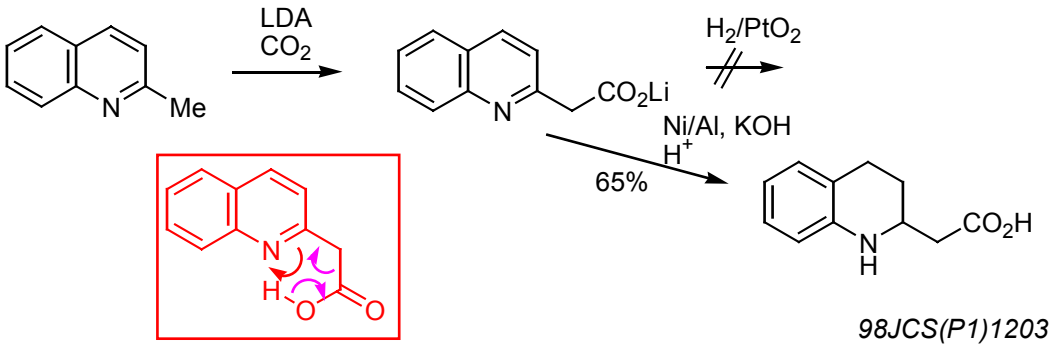
84JOC4203

Selective reduction: quinolines



91JMC2624

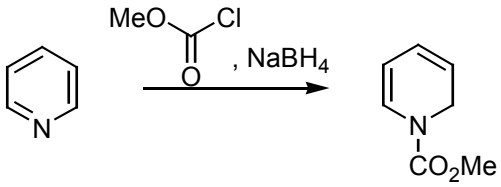
Review and further examples: 96T15031



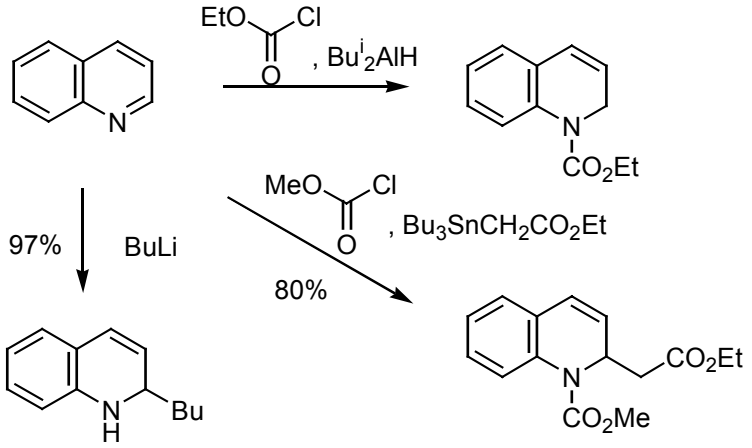
98JCS(P1)1203

Reduction of quinoline and isoquinoline by indium metal: 98SL1029

1,2-Dihydropyridines and 1,2-dihydroquinolines

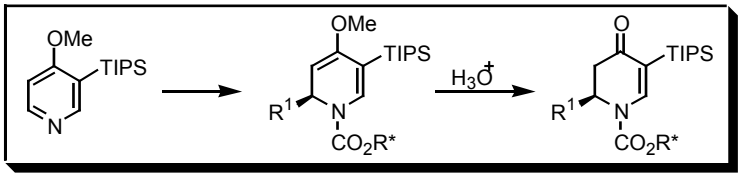


Review and further examples:
Comins, O'Connor, 88AHC(44)199

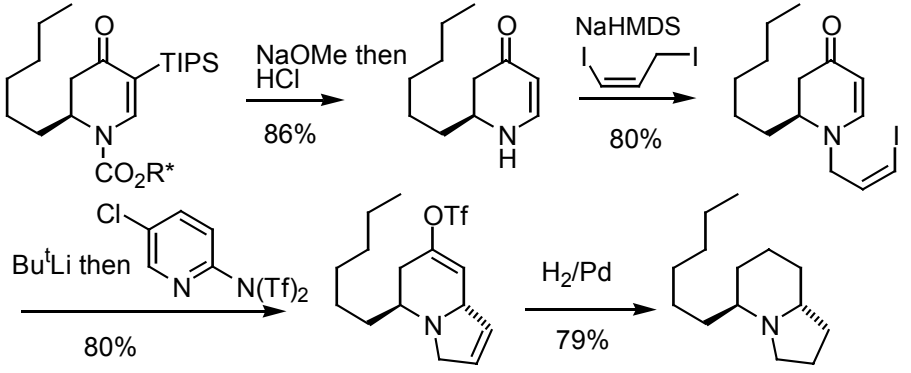


94TL989

An application of the acylation-nucleophilic alkylation sequence

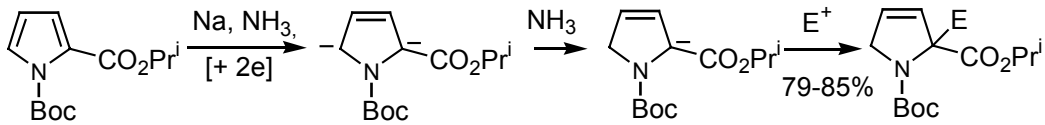


The bulky TIPS (tri-isopropylsilyl) group directs the site of attack of the incoming nucleophile

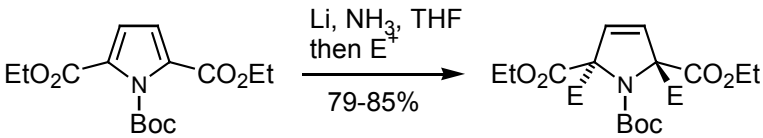


Review: Comins et al., 97PAC477

The Birch reduction of pyrrole esters



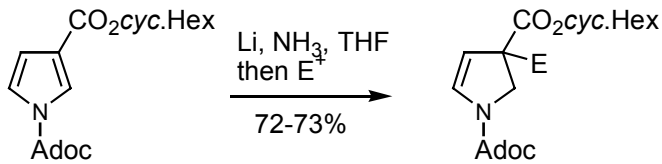
Donohoe, 98JCS(P1)667



About 10:1 *trans*:*cis*

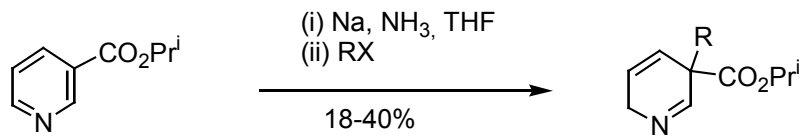
(The two E can be different)

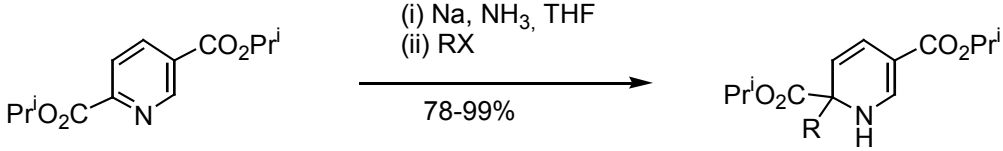
Donohoe, 00TL1327



Donohoe, 98TL3075, 99CC141

The Birch reduction of pyridine esters





Donohoe, 00 OL3861

If you have any comments on this material, particularly suggestions for improving it, please email me: tlg57@liv.ac.uk

Thanks

Tom Gilchrist